BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,
Please do not report the images to the
Image Problem Mailbox.

L Number	Hits	Search Text	DB	Time stamp
1	561	623/1.39 or 623/1.4 or 623/1.42 or 623/1.43 or 623/1.46	USPAT; US-PGPUB; EPO; JPO	2003/07/07 11:17
6	23	(623/1.39 or 623/1.4 or 623/1.42 or 623/1.43 or 623/1.46) and stent and ((inner or interior or lumen$2 or lumin$2) with (rough$4 or texture$2))	USPAT; US-PGPUB; EPO; JPO	2003/07/07 11:50
11	202	(623/1.39 or 623/1.4 or 623/1.42 or 623/1.43 or 623/1.46) and stent and (pores or porous)	USPAT; US-PGPUB; EPO; JPO	2003/07/07 11:37
16	26	(623/1.39 or 623/1.4 or 623/1.42 or 623/1.43 or 623/1.46) and stent and ((pores or porous) with metal$3)	USPAT; US-PGPUB; EPO; JPO	2003/07/07 11:50
21	144	stent and ((inner or interior or lumen$2 or lumin$2) with (rough$4 or texture$2 or friction or porous) with balloon)	USPAT; US-PGPUB; EPO; JPO	2003/07/07 11:54
26	56	stent and ((inner or interior or lumen$2 or lumin$2) with surface with (rough$4 or texture$2 or friction or porous) with balloon)	USPAT; US-PGPUB; EPO; JPO	2003/07/07 13:14
31	1	6254631.URPN.	USPAT	2003/07/07 12:22
32	27	("4733665" | "4739762" | "4776337" | "5019085" | "5195984" | "5342348" | "5419760" | "5421955" | "5443500" | "5449373" | "5476508" | "5514154" | "5540712" | "5569295" | "5591197" | "5649977" | "5695516" | "5697971" | "5707386" | "5707387" | "5718713" | "5725572" | "5728131" | "5741327" | "5800526" | "5810872" | "5853419").PN.	USPAT	2003/07/07 12:22
33	14	5762631.URPN.	USPAT	2003/07/07 13:04
34	18	("1596754" | "3872893" | "4410476" | "4421810" | "4681570" | "4689174" | "4900314" | "5054501" | "5122125" | "5147317" | "5217440" | "5244619" | "5337733" | "5404887" | "5417208" | "5445624" | "5496292" | "5571086").PN.	USPAT	2003/07/07 13:07
36	11	stent and (inner with (liner or graft) with porous)	USPAT; US-PGPUB; EPO; JPO	2003/07/07 13:15
41	9	stent and (inner with (liner or graft) with porous) and balloon	USPAT; US-PGPUB; EPO; JPO	2003/07/07 13:15
-	1	6254631.pn.	USPAT; US-PGPUB; EPO; JPO	2003/07/07 11:16
-	62	623/1.14	USPAT; US-PGPUB; EPO; JPO	2002/06/26 15:39
-	534	623/1.15	USPAT; US-PGPUB; EPO; JPO	2002/06/26 15:40
-	95	623/1.36	USPAT; US-PGPUB; EPO; JPO	2002/06/26 15:41
-	108	623/1.46	USPAT; US-PGPUB; EPO; JPO	2002/06/26 15:42
-	118	623/901 and stent	USPAT; US-PGPUB; EPO; JPO	2002/06/26 15:42
-	117	stent and polish$4 and rough$5 and surface	USPAT; US-PGPUB; EPO; JPO	2002/06/26 16:40
-	806	623/1.14 or 623/1.15 or 623/1.36 or 623/1.46 or (623/901 and stent)	USPAT; US-PGPUB; EPO; JPO	2002/06/26 15:44

-	31	(623/1.14 or 623/1.15 or 623/1.36 or 623/1.46 or (623/901 and stent)) and (stent and polish$4 and rough$5 and surface)	USPAT; US-PGPUB; EPO; JPO	2002/06/26 16:39
-	86	(stent and polish$4 and rough$5 and surface) not (623/1.14 or 623/1.15 or 623/1.36 or 623/1.46 or (623/901 and stent))	USPAT; US-PGPUB; EPO; JPO	2002/06/26 16:39
-	1	stent and polish$4 and (rough$5.ab.) and surface and migration	USPAT; US-PGPUB; EPO; JPO	2002/06/26 16:42
-	7	stent and polish$4 and (rough$5.ab.) and surface and friction	USPAT; US-PGPUB; EPO; JPO	2002/06/26 16:44
-	40	stent and polish$4 and rough$5 and surface and friction	USPAT; US-PGPUB; EPO; JPO	2002/06/26 17:13
-	40	stent and (inner with surface with (rough$5 or textur$4))	USPAT; US-PGPUB; EPO; JPO	2002/06/26 17:46
-	88	(surface with roughness) and stent	USPAT; US-PGPUB; EPO; JPO	2002/06/26 17:58
-	1913	stent and balloon and (adhesive or rough$5 or textur$3)	USPAT; US-PGPUB; EPO; JPO	2002/06/26 18:00
-	129	stent and balloon and (adhesive or rough$5 or textur$3) and (prevent with migration)	USPAT; US-PGPUB; EPO; JPO	2002/06/26 18:02
-	5	stent and balloon and (adhesive or rough$5 or textur$3) and (prevent with migration).ab.	USPAT; US-PGPUB; EPO; JPO	2002/06/26 18:26
-	12	623/1.1 and 623/1.39	USPAT; US-PGPUB; EPO; JPO	2002/06/26 18:30
-	47	623/1.1 and migration and balloon	USPAT; US-PGPUB; EPO; JPO	2002/06/26 18:31
-	78	623/1.11 and migration and balloon	USPAT; US-PGPUB; EPO; JPO	2002/06/26 18:39
-	10	623/1.11 and 623/1.39	USPAT; US-PGPUB; EPO; JPO	2002/06/26 18:31
-	5	623/1.11 and migration and balloon and (rough$6 or textur$4)	USPAT; US-PGPUB; EPO; JPO	2002/06/26 18:34
-	14	623/1.11 and (migration with balloon)	USPAT; US-PGPUB; EPO; JPO	2002/06/26 18:47
-	11	427/23$1 and stent	USPAT; US-PGPUB; EPO; JPO	2002/06/26 19:04
-	65	427/2.28 and stent	USPAT; US-PGPUB; EPO; JPO	2002/06/26 19:05
-	4	427/2.28 and stent and polish$5	USPAT; US-PGPUB; EPO; JPO	2002/06/26 19:06
-	59	stent and ((surface with rough$4) with (luminal or inner or interior))	USPAT; US-PGPUB; EPO; JPO	2002/12/28 14:37
-	6	stent and ((surface with roughness) with (luminal or inner or interior))	USPAT; US-PGPUB; EPO; JPO	2002/12/28 14:11
-	53	(stent and ((surface with rough$4) with (luminal or inner or interior))) not (stent and ((surface with roughness) with (luminal or inner or interior)))	USPAT; US-PGPUB; EPO; JPO	2002/12/28 14:16
-	1	6254631.URPN.	USPAT	2002/12/28 14:27

-	3	stent and (surface with (luminal or inner or interior) with ((increased or enhanced) with friction))	USPAT; US-PGPUB; EPO; JPO	2002/12/28 14:39
-	3	stent and (surface with (luminal or inner or interior) with (increased or enhanced) with friction)	USPAT; US-PGPUB; EPO; JPO	2002/12/28 14:41
-	29	stent and ((surface with textur$3) with (luminal or inner or interior))	USPAT; US-PGPUB; EPO; JPO	2002/12/28 14:42

US006217607B1

(12) **United States Patent**
Alt

(10) **Patent No.: US 6,217,607 B1**
(45) **Date of Patent: Apr. 17, 2001**

(54) **PREMOUNTED STENT DELIVERY SYSTEM FOR SMALL VESSELS**

(75) Inventor: **Eckhard Alt**, Ottobrunn (DE)

(73) Assignee: **Inflow Dynamics Inc.**, Springfield, VA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/366,287**

(22) Filed: **Aug. 2, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/259,906, filed on Feb. 28, 1999, and a continuation-in-part of application No. 09/175,919, filed on Oct. 20, 1998, now Pat. No. 6,099,561.

(51) **Int. Cl.**[7] **A61F 2/06**

(52) **U.S. Cl.** **623/1.1**; 606/192; 623/1.46

(58) **Field of Search** 606/192, 108, 606/194, 195, 198; 604/96; 623/1.1, 1.44, 1.46

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,645,560 * 7/1997 Crocker et al. 606/192

6,027,517 * 2/2000 Crocker et al. 606/108

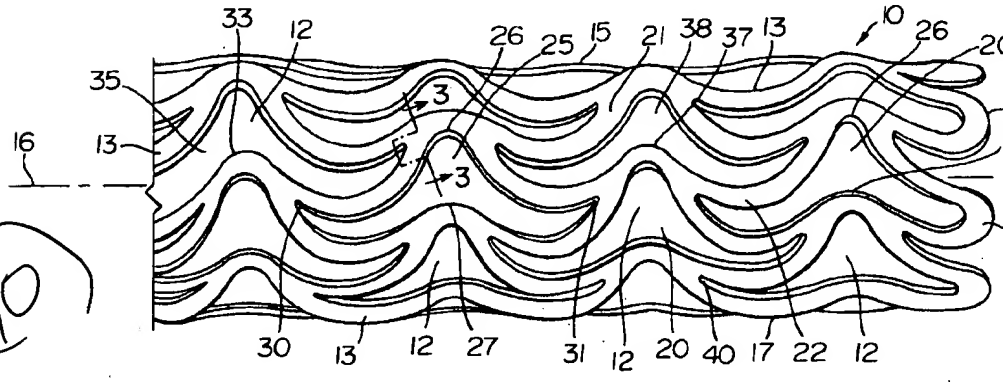
* cited by examiner

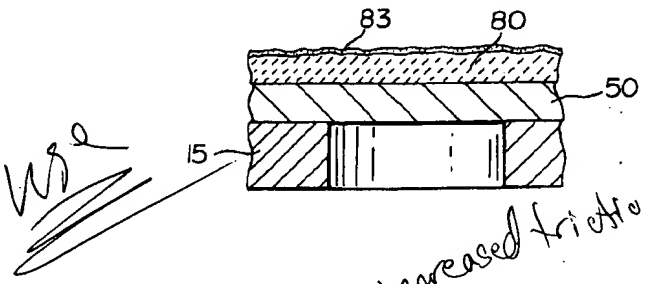
Primary Examiner—Kevin Truong

(57) **ABSTRACT**

A stent delivery system is sized to allow it to traverse small-sized vessels of diameter in a range from about 1.25 mm to less than about 2.5 mm in a human body. The delivery system includes a balloon which has an inflated diameter less than 2.5 mm at nominal pressure and is integrated distally on a catheter for selective inflation and deflation through a lumen of the catheter. The stent is adapted to be mounted on the uninflated balloon so that the combination of the balloon when uninflated and the stent mounted thereon has a crossing profile in a range from approximately 0.5 mm to approximately 0.8 mm, to enable the delivery system to rapidly traverse the small-sized vessel for subsequent deployment of the stent at a preselected target site of the vessel. At the target site, the balloon is inflated to expand the diameter of the stent to lodge against the wall of the vessel and remain in place when the balloon is deflated and the delivery system is withdrawn from the vessel. The stent has a coating with a surface feature that increases the retention of the stent on the balloon during advancement of the stent delivery system through the vessel.

18 Claims, 1 Drawing Sheet





US005972027A

United States Patent [19]

Johnson

[11] Patent Number: 5,972,027

[45] Date of Patent: Oct. 26, 1999

[54] **POROUS STENT DRUG DELIVERY SYSTEM**

[75] Inventor: **Michael W. Johnson**, Plymouth, Minn.

[73] Assignee: **Scimed Life Systems, Inc**, Maple Grove, Minn.

[21] Appl. No.: **08/940,696**

[22] Filed: **Sep. 30, 1997**

[51] **Int. Cl.**[6] **A61F 2/06**

[52] **U.S. Cl.** **623**/1; 623/12; 424/422; 424/423

[58] **Field of Search** 623/1, 11, 12, 623/16; 606/108, 191, 194, 195, 198; 424/422, 423

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,073,999	2/1978	Bryan et al.	428/311
4,082,893	4/1978	Okita	428/376
4,101,984	7/1978	MacGregor	3/1.5
4,208,745	6/1980	Okita	623/1
4,222,977	9/1980	Dobo	264/63
4,405,319	9/1983	Cosentino	604/175
4,770,664	9/1988	Gogolewski	623/66
4,784,159	11/1988	Szilagyi	128/784
4,784,160	11/1988	Szilagyi	128/784
4,850,999	7/1989	Planck	623/1
5,019,090	5/1991	Pinchuk	606/194
5,059,166	10/1991	Fischecll et al.	600/3
5,104,403	4/1992	Brotuzu et al.	623/1
5,116,360	5/1992	Pinchuk et al.	623/1
5,132,080	7/1992	Pfeil	419/2
5,163,958	11/1992	Pinchuk	623/11
5,176,617	1/1993	Fishell et al.	600/3
5,222,971	6/1993	Willard et al.	606/158
5,226,913	7/1993	Pinchuk	623/1
5,234,458	8/1993	Metais	606/200
5,342,348	8/1994	Kaplan	604/891.1
5,383,928	1/1995	Scott et al.	623/1
5,449,382	9/1995	Dayton	623/1
5,618,298	4/1997	Simon	606/194
5,641,443	6/1997	Calcote et al.	264/127
5,707,385	1/1998	Williams	606/192
5,749,880	5/1998	Banas et al.	606/198
5,769,884	6/1998	Solavay	623/12
5,772,748	6/1998	Hubbard	106/38.27
5,817,126	10/1998	Imran	623/12
5,843,172	12/1998	Yan	623/1
5,855,600	1/1999	Alt	623/12
5,882,335	3/1999	Leone et al.	604/96

FOREIGN PATENT DOCUMENTS

90/13332	11/1990	WIPO	A61M 31/00
WO 91/17789	11/1991	WIPO	A61M 29/02
96/01733	1/1996	WIPO	B32B 3/10
WO 96/00103	1/1996	WIPO	A61M 29/00
96/32907	10/1996	WIPO .	
98/32412	7/1998	WIPO .	

OTHER PUBLICATIONS

J. Kroschwitz, ed., Concise Encyclopedia of Polymer Science and Engineering, p. 1167, 1990.

K.H. Roll, Kirk–Othmer Concise Dictionary of Chemical Technology, pp. 945–947, 1985.

FILTERMET product literature. Date unknown.

Primary Examiner—Mickey Yu

Assistant Examiner—Tram A. Nguyen

Attorney, Agent, or Firm—Vidas, Arrett & Steinkraus

[57] **ABSTRACT**

Expandable intraluminal stents made of a powdered metal or polymer are provided as well their method of manufacture. These stents are characterized by a desired porosity, with a drug compressed into the pores of the stent. The stents are formed by subjecting one or more powdered materials in a die cavity to a pressure treatment followed by a heat treatment. The material may be cast directly in a stent-like form or cast into sheets or tubes from which the inventive stents are produced. The so-formed porous metal or polymer stent is then loaded with one or more drugs.

9 Claims, 3 Drawing Sheets

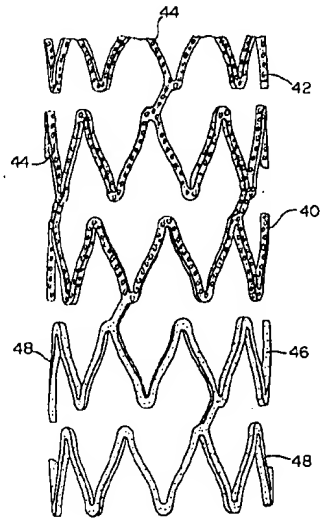


Fig. 1a

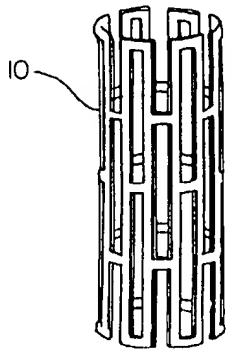


Fig. 1b

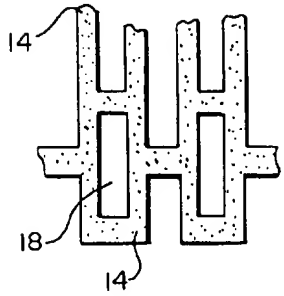


Fig. 2

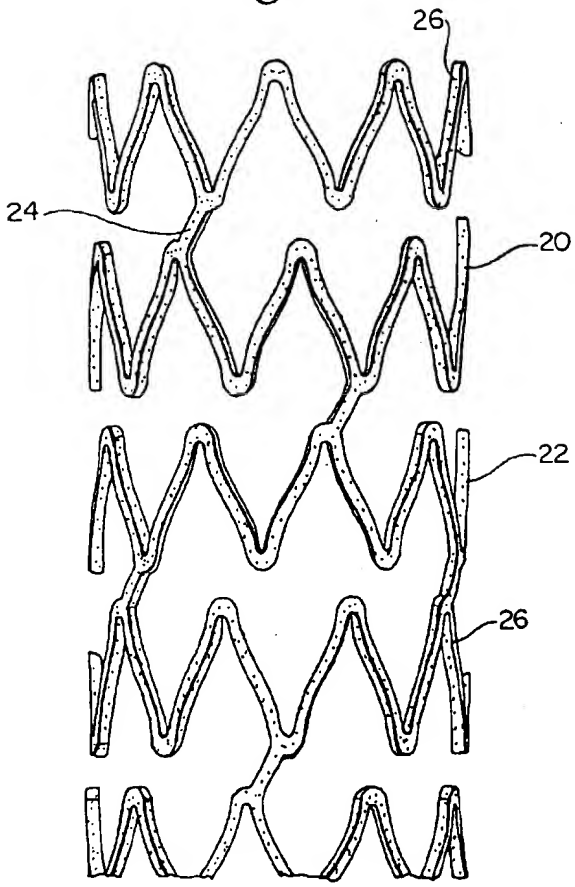


Fig. 3

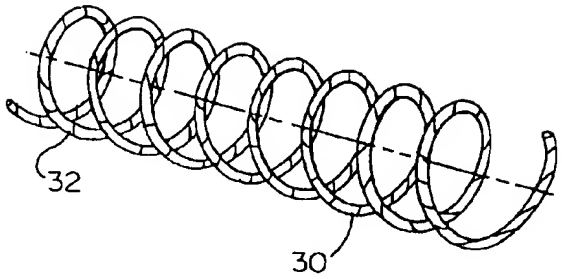


Fig. 4a

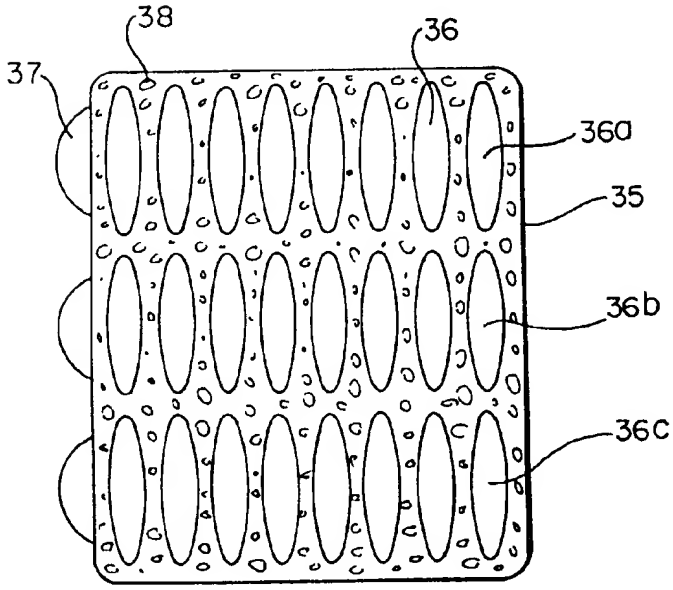


Fig. 4b

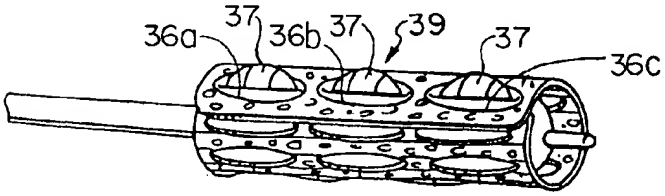
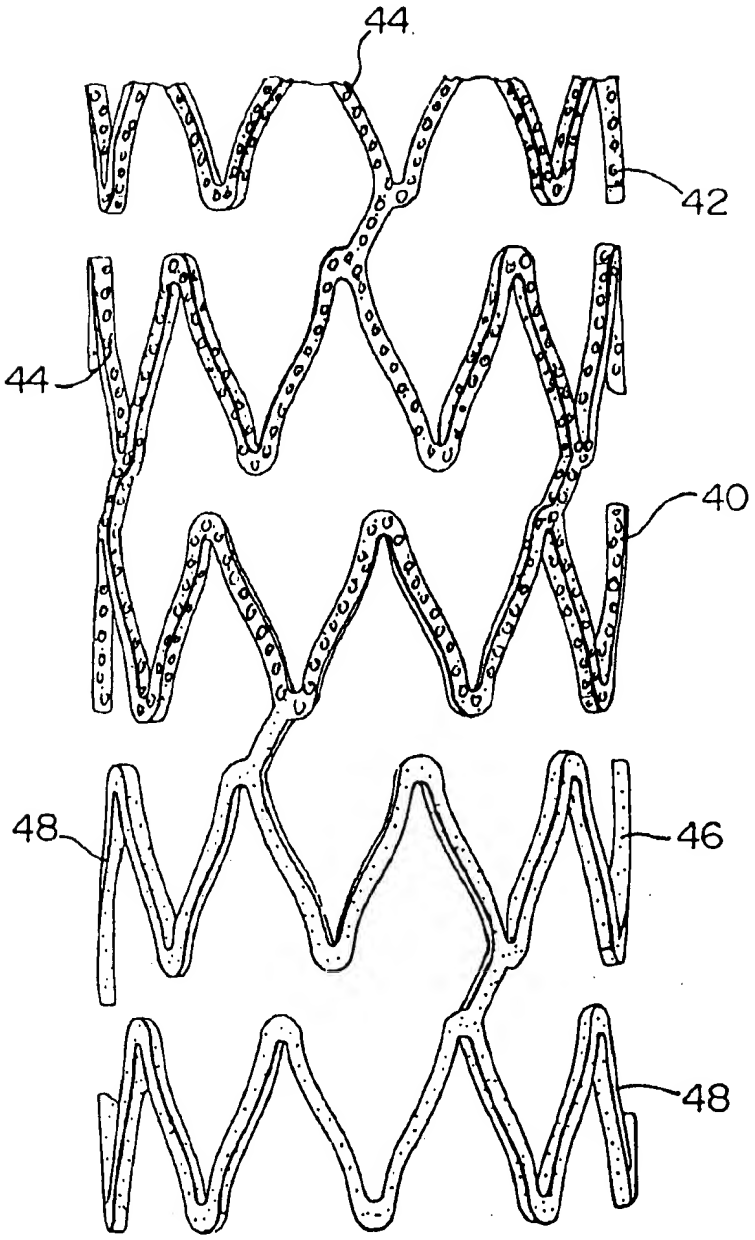


Fig. 5



POROUS STENT DRUG DELIVERY SYSTEM

BACKGROUND OF THE INVENTION

This invention relates to stents for maintaining the patency of body passages. Additionally, the stents may serve as drug delivery vehicles. The invention has particular application to stenting in blood vessels of the human body and will be described with reference thereto. However, in a broader sense it relates to stenting in any body passage, including such passages as the gastrointestinal tract, urethral and ureteral tracts, bronchial and esophageal tracts. The invention also has particular reference to stents comprising compounds useful for the treatment and prevention of restenosis and also will find application in dilating and maintaining the patency of various body passages such as ureters and the like.

SUMMARY OF THE INVENTION

In accordance with the present invention, a porous stent made from a powdered metal or polymeric material is disclosed. The inventive stent is an expandable intraluminal stent comprising a main body portion having a first end, a second end and a flow passage defined therethrough, the main body portion being sized for intraluminal placement within a body passage and subsequent expansion for implantation. The main body portion of the stent of the present invention is further characterized in that it is formed at least in part of at least one porous material, the porous material having been formed from a powdered metal or polymeric material.

In another embodiment of the present invention, a drug is contained within the pores of the stent for delivery to the body.

In another embodiment of the present invention, the stent may be coated with a drug.

In another embodiment of the present invention, the stent is comprised of at least two porous metals.

The present invention is also directed to a method for making a porous expandable intraluminal stent comprising the steps of providing a powdered material, subjecting the powdered material to high pressure to form a compact, sintering the compact to form a final porous material and forming a stent from the porous material. In another embodiment of the above-mentioned inventive method, at least one drug is loaded into the pores of the stent.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1***a* is a perspective view of one embodiment of a stent according to the present invention.

FIG. 1*b* is an enlargement of a portion of FIG. 1*a* showing pores on the surface of the metal.

FIG. **2** is a sectional view of another embodiment of a stent in accordance with this invention.

FIG. **3** is a perspective view of another embodiment of a stent according to the present invention.

FIG. **4***a* is a plan view development of the inventive stent in sheet form prior to rolling.

FIG. **4***b* is a sectional view of another embodiment of a stent according to the present invention.

FIG. **5** is a perspective view of yet another embodiment of a stent according to this invention.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EXEMPLARY EMBODIMENTS

The present invention relates to a porous stent made from a powdered material such as powdered metal or polymer for

maintaining the patency of body passages. Stents to which the present invention relates may be either balloon expandable or self-expanding as well as springy in form. For example, self-expanding stents are known which are braided, woven or mesh-like in structure, although many other types of self-expanding stents including solid stents are also known. Such stents have memory characteristics and, if distorted in length and/or diameter by external forces, they will return or tend to return to a preformed configuration upon the release of external forces. This expansion may be due to the natural springiness of the stent, for instance with a rolled up sheet stent, or as a result of a phase transition occurring in the stent material. Balloon expandable stents may be expanded by the application of a suitable amount of force to the stent.

The stents of the present invention may be used to deliver drugs to a desired bodily location. As used in this application, the term "drug" denotes any compound which has a desired pharmacologic effect, or which is used for diagnostic purposes. Useful drugs, in the context of the present invention include, but are not limited to angiogenic drugs, smooth muscle cell inhibitors, collagen inhibitors, vasodilators, anti-platelet substances, anti-thrombotic substances, anti-coagulants, cholesterol reducing agents and combinations thereof. The drugs may include radiochemicals to irradiate and/or prohibit tissue growth or to permit diagnostic imaging of a site.

The porous stent may be used as a drug-delivery system to, for example, prevent restenosis. The drugs may include radiochemicals to irradiate and prohibit tissue growth. Angioplasty and stent deployment may cause injury of the endothelial cell layer of blood vessels, causing smooth muscle cell proliferation, leading to restenosis. To control smooth muscle cell growth endothelialization of cells on the inner wall surface of vessels will prevent or prohibit the smooth muscle growth. To promote endothelialization human growth factors may be included in the outer layer and delivered.

The stent of the present invention may be formed of any bio-compatible powdered metals such as stainless steel. Powdered metals typically are available in powder sizes as small as 40 microns or less. While powdered metals of any powder size may be used in forming the stents of the present invention, preferably powders 40 microns or less will be used in forming the porous metal stent of the present invention. More preferably, powdered metals ranging in size from 6 to 12 microns will be used. Especially desirable are powders with good flow properties so that the particles may be dispensed easily into a die cavity for metal processing. Other suitable metals include, but are not limited to, spring steel, nitinol and titanium as well as any other bio-compatible metal which may become available in powdered form in the future. Suitable metals do not produce toxic reactions or act as carcinogens. The stent of the present invention may also be formed of bio-compatible powdered polymeric materials such as PTFE.

The stents of the present invention may also be prepared with different mean pore sizes. Pore size is an important parameter in that certain macromolecular drugs may be excluded from use where the pore size is very small. The pore size may also play a role in determining the extent of cellular infiltration or tissue ingrowth during implantation of the stent. While cellular ingrowth is sometimes desirable, it can also lead to complications such as infection and difficulty in removing the stent. Stents with a mean pore size of greater than about 10 microns can allow infiltration of cellular sized biomaterials; stents with mean pore sizes in

the range of 1–10 microns may accommodate infiltration of some of the above bio-materials. Stents with pore sizes less than about 1 micron will not generally accommodate infiltration of any of the above biomaterials but can accommodate infiltration of macromolecular and small biomaterials. Thus, the pore size of the stent may be varied to foster or inhibit cellular infiltration and/or tissue ingrowth. Of course, the pore size may also be varied to facilitate delivery of drugs of different molecular sizes.

The material processing proceeds with a pressure treatment step in which the powdered material in a die cavity is subjected to pressures of up to twenty tons or more. At such high pressures, the powder begins to interlock, forming a compact with pockets of air remaining in the metal. The pressure treatment step usually proceeds at room temperature although warm or hot pressing may be used. Other techniques to form the compact, as known in the art, may be substituted for the pressure treatment step. The die cavity used in this step may be a stent die cavity to allow for direct casting of the stent or alternatively, may be for some other form such as a tube or a sheet. Following the pressure treatment step, the compact has sufficient strength to allow for routine handling without breakage.

After ejection from the die, the compact is sintered to form a coherent metal or polymer mass in the shape of the die. Alternatively, the pressure treatment step can be eliminated and the processing limited to a sintering in which the metal or polymer powder is heated in a die resulting in a low density, highly porous compound. Although the sintering step may actually partially melt the metal or polymer as in liquid-phase sintering, in the preferred embodiment, the sintering step does not melt the metal or polymer as the temperature is maintained below the melting point of elemental metal or any alloys that have formed or the polymer melting point. The sintered metal or polymer will exhibit a porosity ranging from less than 10 percent to about 80 percent of the total volume. The percentage porosity is a measure of the void space within the metal.

Following sintering, the now porous metal or polymer may be formed into a stent, if it has not been so-formed already. Any known process in the art may be used including laser cutting and braiding of porous metal strands. FIGS. **1***a* and **1***b* illustrate one such stent **10**, with pores **14** formed by laser cutting apertures **18** in a sheet of porous metal. FIG. **2** illustrates a stent **20** which is composed of a number of interconnected members **22**, the members and interconnections **24** made of a metal containing pores **26**. A braided stent may be formed of a series of strands arranged in a crossing configuration which may be woven, braided or the like. The strands of porous metal or polymer can be deformed so to provide a reduced diameter of the stent which facilitates its delivery to the targeted portion of a vessel or other passageway and once disposed at the target portion the stent can then be allowed to expand to its preformed configuration and larger diameter.

The stents of the present invention may be prepared in a range of porosities allowing for the production of stents with differing drug delivery characteristics. The porosity may be between twenty and eighty percent of the total volume and more suitably between forty and sixty percent of the volume.

The stent may be impregnated with one or more drugs by any known process in the art including high pressure loading in which the stent is placed in a bath of the desired drug or drugs and subjected to high pressure or, alternatively, subjected to a vacuum. The drug may be carried in a volatile or non-volatile solution. In the case of a volatile solution, following loading of the drug, the volatile carrier solution may be volatilized. In the case of the vacuum, the air in the pores of the metal stent is evacuated and replaced by the drug-containing solution.

In accordance with the present invention, the stent may further be coated with one or more layers of one or more drugs to allow for longer term drug elution optionally employing a number of different drugs over time. As such, the drug in the pores would not be eluted until the coating of drug has been absorbed, thereby allowing for longer term drug treatment than would be available from the coated metal alone.

FIG. **3** shows a coil stent **30** in which the porous metal stent **30** further comprises such a coating **32** (the pores have been omitted for clarity).

The inventive stent may also be formed from a rolled up flat sheet comprised of a porous metal or polymer as shown in FIG. **4***a*. The sheet **35** contains a plurality of apertures **36** and pores **38** as well as tabs **37**. The tabs are inserted into the holes **36***a–c* when the stent is rolled, as shown generally at **39** in FIG. **4***b*. The stent may be rolled tightly for delivery and implantation and be self-expandable to the extent that it tends to unroll. The stent may further be laminated with a layer of drug over the porous surface of the stent. Otherwise, it may simply be expanded by independent expansion means such as a balloon catheter positioned inside the stent as is already known in the art.

Another embodiment of the invention contemplates the fabrication of any stent design per se taken from the prior art, the stent prepared from a porous metal or polymer, the pores of the metal or polymer including one or more drugs.

Another embodiment of the invention is an expandable intraluminal stent comprising a main body portion having a first end, a second end and a flow passage defined therethrough, the main body portion being sized for intraluminal placement within a body passage and subsequent expansion for implantation, the main body portion being further characterized in that it is formed at least in part of at least two metals, the two metals comprising a first porous metal characterized by a first porosity and mean pore size and a second porous metal characterized by a second porosity and mean pore size. FIG. **5** depicts one such stent, **40**, the first metal **42** containing first pores **44** therein and the second metal **46** containing second pores **48** therein.

In the above embodiment, one drug may be loaded into the pores of the first porous metal and a second drug loaded into the pores of the second porous metal. Alternatively, the same drug can be loaded into both the first and second porous metals.

The present invention is also directed to a method for making a porous metal, expandable intraluminal stent comprising the steps of providing a powdered metal or polymeric material, subjecting the powder to high pressure to form a compact, sintering the compact to form a final porous metal or polymer, forming a stent from the porous metal and, optionally, loading at least one drug into the pores. The drug(s) may be loaded into the pores by placing the stent in a liquid bath comprising the at least one drug at high pressure, by placing the stent in a liquid bath within a chamber, the liquid bath comprising the drug(s), and reducing the pressure within the chamber below ambient pressure or by any other method known in the art.

In yet another embodiment, the invention is directed to a method of making an expandable intraluminal stent of varying porosity comprising the steps of providing two or more metal and/or polymeric powders in a die, subjecting

the two or more powders to high pressure to form a compact, sintering the compact to form a final porous metal or polymer of varying porosity, forming a stent from the porous metal or polymer and, optionally, loading at least one drug into the pores. The two or more powdered metals and/or polymers can comprise at least two different metals and/or polymers or can comprise one metal or polymer, the one metal or polymer provided in at least two different average particle sizes or can comprise several different metals or polymers provided in several different average particle sizes. In such a way, the porosity of the stent in different regions of the stent can be tailored by forming the stent of several different powdered metals or polymers comprising a combination of different elemental metals or alloys or polymers in powdered form, or using the same elemental metal, alloy or polymer but providing it in several powders of different average particle size or by some combination of different metals and/or polymers and same metals and/or polymers of different particle size.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiments, it is to be understood that the invention is not to be limited to the disclosed embodiments but, on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

The above Examples and disclosure are intended to be illustrative and not exhaustive. These examples and description will suggest many variations and alternatives to one of ordinary skill in this art. All these alternatives and variations are intended to be included within the scope of the attached claims. Those familiar with the art may recognize other equivalents to the specific embodiments described herein which equivalents are also intended to be encompassed by the claims attached hereto.

What is claimed is as follows:

1. An expandable intraluminal stent comprising a main body portion having a first end, a second end and a flow passage defined therethrough, the main body portion being sized for intraluminal placement within a body passage and subsequent expansion for implantation, at least a portion of the main body portion formed of at least one material having pores therein, the material having been formed from at least one powdered metal, the stent comprising at least two separate regions arranged along the length of the stent, the first region formed of a first material having first pores within, the first material characterized by a first porosity and a first mean pore size, the first material having been formed from a first powdered metal, the second region formed of a second material having second pores within, the second material characterized by a second porosity and a second mean pore size, the second material having been formed from a second powdered metal.

2. The stent of claim **1** wherein at least one of the first and second regions has a porosity of twenty to eighty percent by volume.

3. The stent of claim **2** wherein at least one of the first and second regions has a porosity of between forty and sixty percent of the total volume of the metal.

4. The stent of claim **1** formed of a plurality of strands of a metal, the metal having pores therein.

5. The stent of claim **1** wherein the stent is coated with one or more layers of one or more drug containing materials.

6. The stent of claim **1** wherein the first or second powdered metal is stainless steel.

7. The stent of claim **6** wherein the pores in the first and second materials contain at least one drug.

8. The stent of claim **7** wherein the drug is selected from the group consisting of smooth muscle cell inhibitors, collagen inhibitors, vasodilators, anti-platelet substances, anti-thrombotic substances, anti-coagulants, cholesterol reducing agents, angiogenics and combinations thereof.

9. The stent of claim **1** wherein the first pores contain a first drug and the second pores contain a second drug.

* * * * *

US006240616B1

(12) **United States Patent**
Yan

(10) **Patent No.: US 6,240,616 B1**
(45) **Date of Patent: *Jun. 5, 2001**

(54) **METHOD OF MANUFACTURING A MEDICATED POROUS METAL PROSTHESIS**

(75) Inventor: **John Y. Yan**, Los Gatos, CA (US)

(73) Assignee: **Advanced Cardiovascular Systems, Inc.**, Santa Clara, CA (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/837,993**

(22) Filed: **Apr. 15, 1997**

(51) **Int. Cl.**[7] **B21B 1/46**

(52) **U.S. Cl.** **29/527.2**; 623/1.42; 623/1.46; 623/1.44; 623/1.39; 419/2

(58) **Field of Search** 29/527.2, 428; 623/1.42, 1.46, 1.47, 1.48, 1.44, 1.39, 1.4, 1.49, 1.54; 419/2

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,855,638		12/1974	Pilliar .	
4,374,669		2/1983	Mac Gregor .	
4,729,871	*	3/1988	Morimoto	419/2
5,163,958		11/1992	Pinchuk .	
5,370,682	*	12/1994	Schmitt	623/1.52
5,370,684		12/1994	Vallana et al. .	
5,437,834	*	8/1995	Okimatsu et al.	419/24
5,492,768	*	2/1996	Okimatsu et al.	419/24
5,522,894		6/1996	Draenert .	
5,624,411		4/1997	Tuch .	
5,630,840		5/1997	Mayer .	
5,632,779		5/1997	Davidson .	
5,755,771	*	5/1998	Penn et al.	623/1.52
5,879,398	*	3/1999	Swarts et al.	623/22.21
5,945,029	*	8/1999	Scholz et al.	264/639
5,972,027	*	10/1999	Johnson	623/1.52

FOREIGN PATENT DOCUMENTS

WO 94/13268	6/1994	(WO) .
WO 95/11817	5/1995	(WO) .
WO 96/28115	9/1996	(WO) .

OTHER PUBLICATIONS

Lambert, Thomas L., M.D., et al., Localized Arterial Wall Drug Delivery From a Polymer–Coated Removable Metallic Stent, *Circulation*, Eol. 90, No. 2 (Aug. 1994) pp. 1003–1011.

De Scheerder, Ivan K, et al., Biocompatibility of Polymer–Coated Oversized Metallic Stents Implanted in Normal Porcine Coronary Arteries, *Atherosclerosis*, vol. 114 (1995) pp. 105–114.

* cited by examiner

Primary Examiner—S. Thomas Hughes
Assistant Examiner—Marc Jimenez
(74) *Attorney, Agent, or Firm*—Fulwider Patton Lee & Utecht, LLP

(57) **ABSTRACT**

A method of manufacturing a medicated prosthesis such as a stent. The method includes forming a stent out of porous metal and loading a therapeutic agent into the pores of the metal. In one embodiment the stent is formed from a sintered metal wire, sheet, or tube and can include adding a coating to the stent. When the stent is implanted into the vasculature of a patient, the therapeutic agent in the stent dissipates into the tissue of the vasculature proximate the stent.

38 Claims, 5 Drawing Sheets

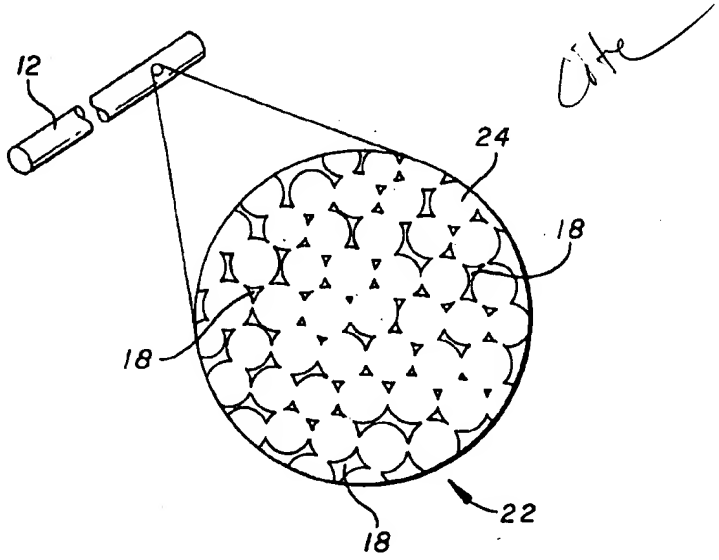
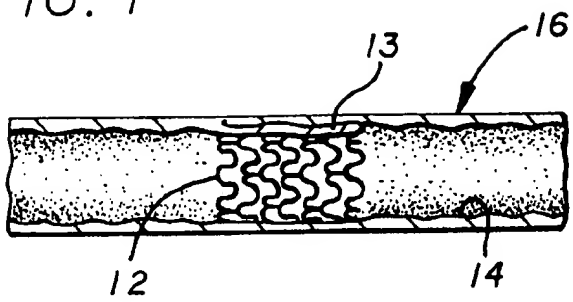


FIG. 1



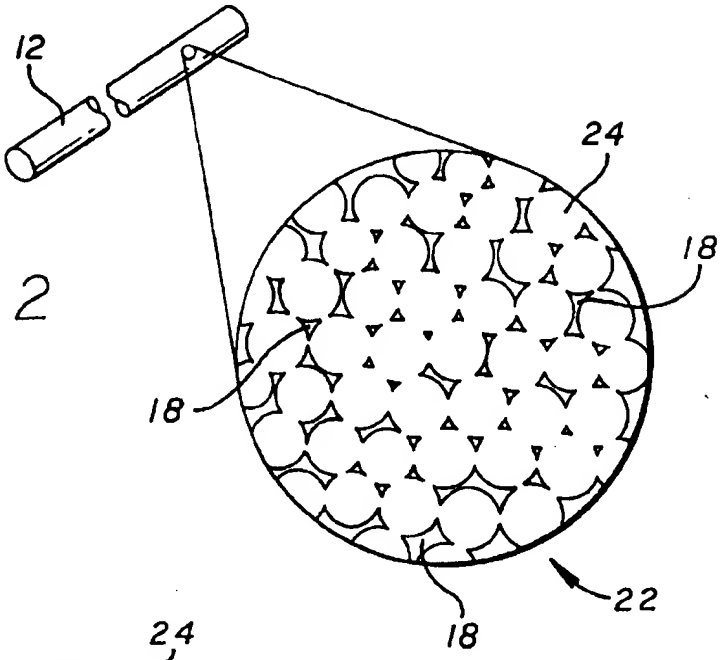


FIG. 2

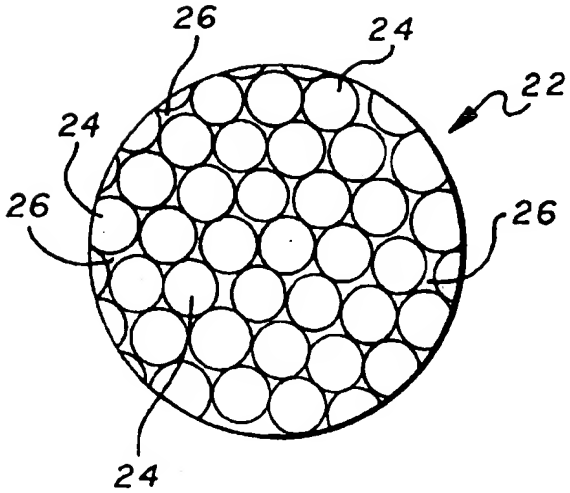
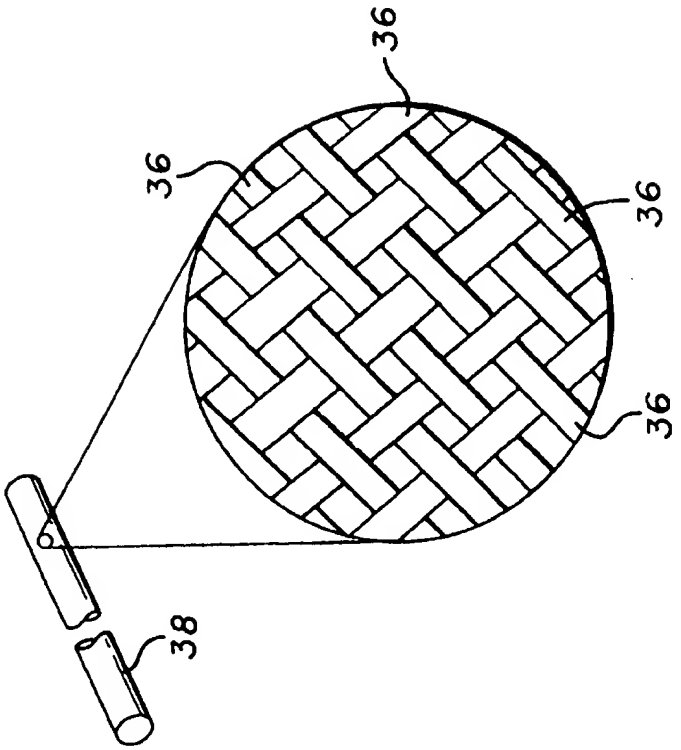


FIG. 3

FIG. 5



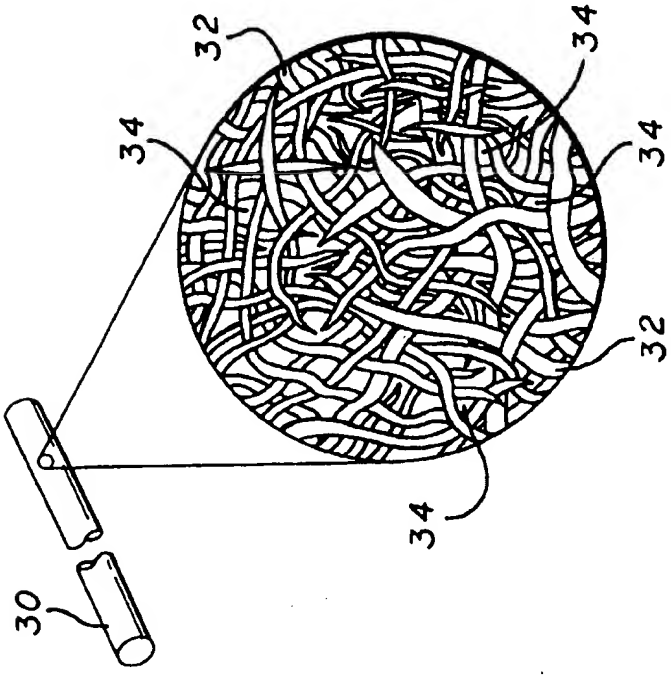


FIG. 4

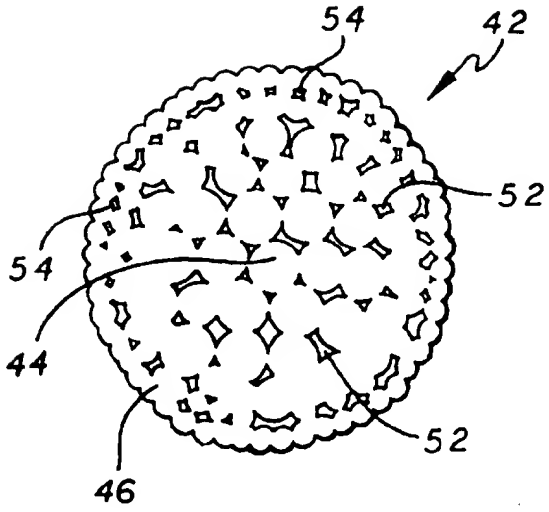


FIG. 6

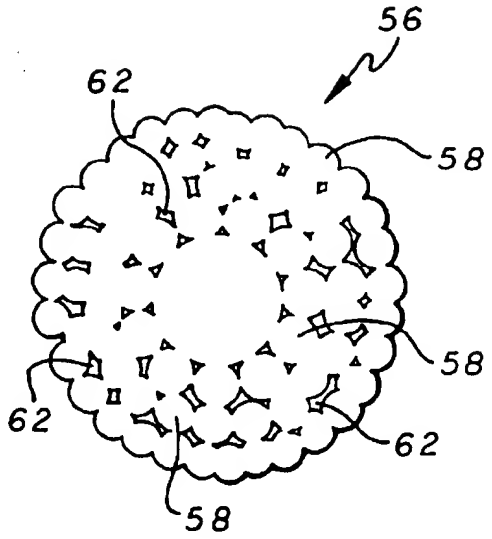


FIG. 7

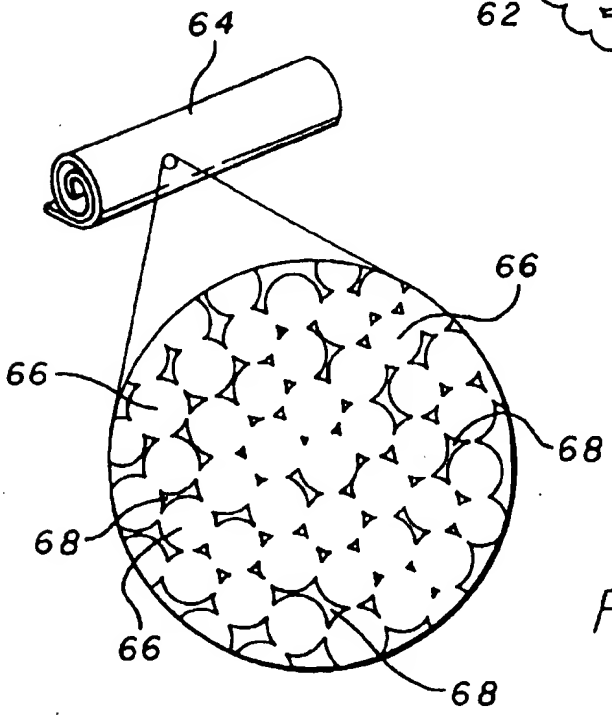
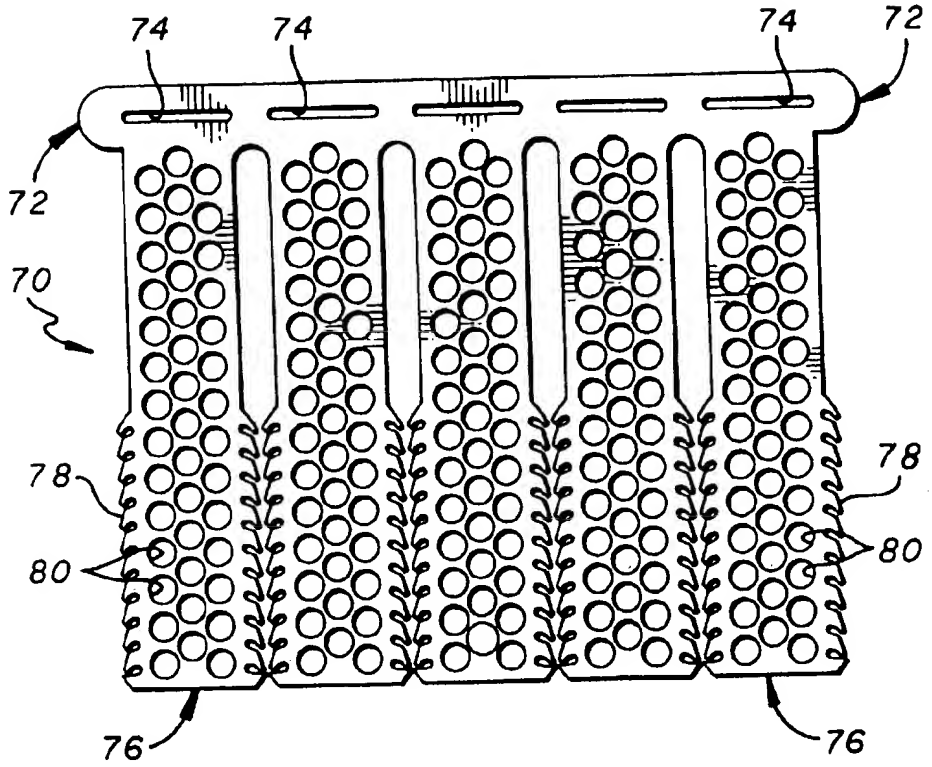


FIG. 8

FIG. 9


74
74
74
72
72
70
78
78
80
80
76
76

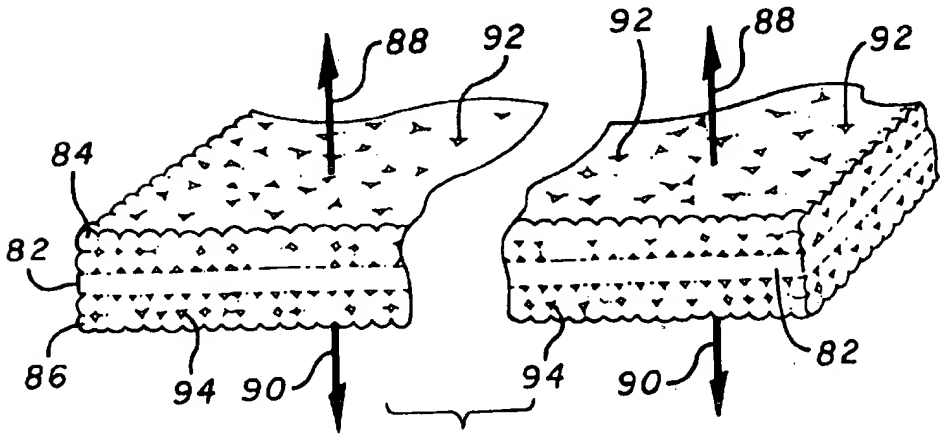

88
92
92
88
92
84
82
86
94
90
94
90
82

FIG. 10

FIG. 11

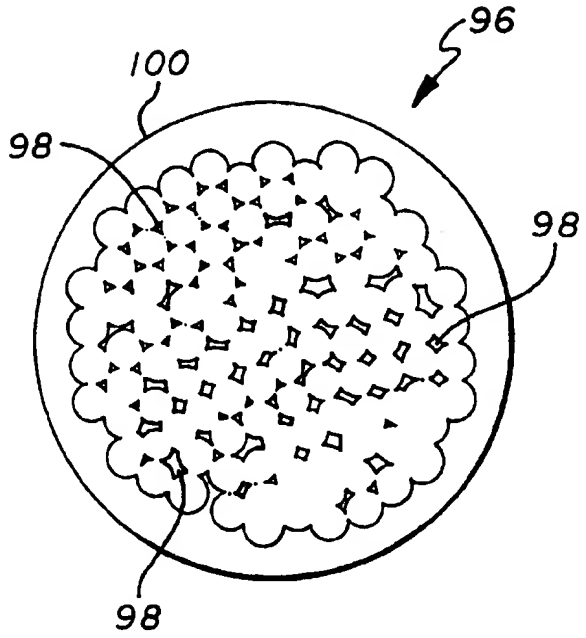
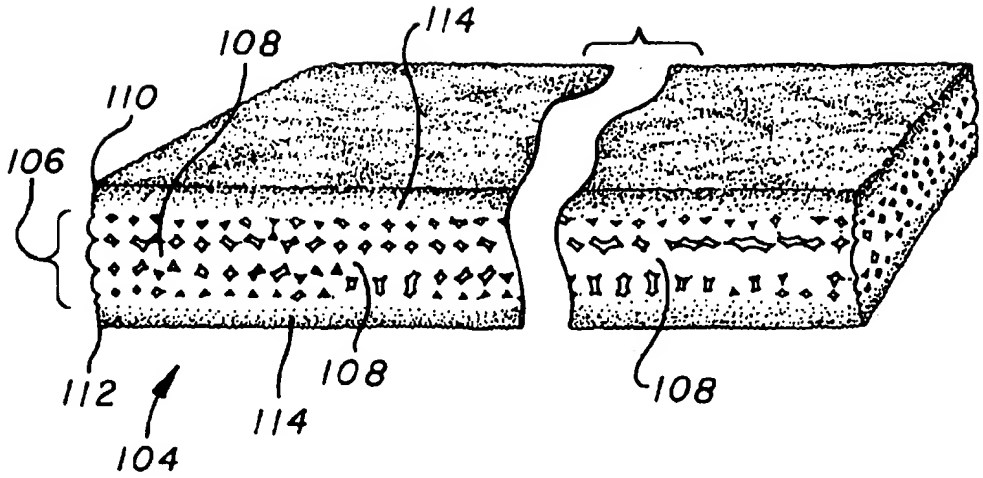


FIG. 12



METHOD OF MANUFACTURING A MEDICATED POROUS METAL PROSTHESIS

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention generally relates to a medicated prosthesis or implant. More particularly, the invention relates to a medicated intra-vascular prosthesis, such as a stent, that is radially expandable in the vasculature of a patient and delivers a therapeutic agent to the site of the implantation.

2. Description of Related Art

Stents are generally cylindrically shaped prosthetic implants which function to hold open and sometimes expand a segment of a blood vessel or other anatomical lumen. They are particularly suitable for supporting and preventing a torn or injured arterial lining from occluding a fluid passageway. Intravascular stents are increasingly useful for treatment of coronary artery stenoses, and for reducing the likelihood of the development of restenosis or closure after balloon angioplasty.

The success of a stent can be assessed by evaluating a number of factors, such as thrombosis; neointimal hyperplasia, smooth muscle cell migration and proliferation following implantation of the stent; injury to the artery wall; overall loss of luminal patency; stent diameter in vivo; thickness of the stent; and leukocyte adhesion to the luminal lining of stented arteries. However, the chief areas of concern are early subacute thrombosis, and eventual restenosis of the blood vessel due to intimal hyperplasia.

Therapeutic pharmacological agents have been developed to improve successful placement of the stent and are delivered to the site of stent implantation. Stents that are of a common metallic structure were previously unable to deliver localized therapeutic pharmacological agents to a blood vessel at the location being treated with the stent. There are polymeric materials that can be loaded with and release therapeutic agents including drugs or other pharmacological treatments which can be used for drug delivery. However, these polymeric materials may not fulfill the structural and mechanical requirements of a stent, especially when the polymeric materials are loaded with a drug, since drug loading of a polymeric material can significantly reduce the structural and mechanical properties of the polymeric material.

It has been known in the art to coat a metallic stent with a polymeric material and load the polymeric material with a drug. Alternatively stents of polymeric materials have been reinforced with metal structure. These stent designs have the strength necessary to hold open the lumen of the vessel because of the reinforced strength of the metal. Stents made of both polymeric material and metal have a larger radial profile because the volume occupied by the metal portion of the stent cannot absorb and retain drugs. Reducing the profile of a stent is preferable because it increases the in vivo diameter of the lumen created by the stent. Thus it is desirable to configure a metallic stent to deliver drugs to the blood vessel walls without substantially increasing the profile of the stent. The present invention meets these needs.

SUMMARY OF THE INVENTION

Briefly and in general terms, the present invention is a method of manufacturing a medicated prosthesis. The method comprises providing a porous metal material having a plurality of porous cavities, forming the material into a prosthesis having a plurality of porous cavities, and loading

therapeutic agents into the pores of the prosthesis. In one embodiment, the prosthesis is a stent for implantation into a blood vessel, biliary duct, esophagus or other body lumen. In one embodiment, the method comprises sintering metal particles including spherical particles, filaments or fibers into a wire, a sheet or tube. Then, the wire, sheet, or tube is further manufactured by forming the stent from the same. Sheets or tubes can be formed into stents by chemical etching or laser cutting the same according to a stent pattern. In another embodiment, the sheet is formed by weaving metallic fibers and sintering the metallic fibers in a metal wire or a sheet.

In yet another embodiment, a sheet of stent material is formed in a plurality of layers. A layer of large diameter particles are arranged in a first horizontal plane. Two layers of small diameter particles are arranged on both sides of the plane. The particles are sintered into a sheet of particles that has a large core formed of large diameter particles sandwiched between two layers of small diameter particles. Similarly, a sintered stent wire can be formed by arranging large diameter particles along a first axis and then arranging small diameter particles radially outward from and coaxial to the large diameter particles. Then, the particles are sintered to form a stent wire that has a substantially porous central cavity and an outer layer that has smaller pore diameter.

In yet another embodiment, the method of forming a stent comprises arranging a sheet of solid metal between two layers of particles. The particles are then sintered to both sides of the sheet. Similarly, the particles can be sintered to one side of the metal sheet. Alternatively, particles can be oriented radially outward from a solid metal wire and sintered into a partially porous wire. The partially porous wire and the stent with a sheet metal core are believed to improve the strength of the overall stent.

According to one embodiment of the present invention, a therapeutic agent can be loaded into the pores of the stent by immersing the stent in a liquid solution containing the therapeutic agent. The stent is emersed for a period of time sufficient to permit therapeutic agent to be absorbed into the porous cavities of the stent. The therapeutic agent may be any number of drugs or chemical agents that treat arterial diseases and stent implantation side effects.

In yet another embodiment of the invention the method includes coating the stent with a polymer. The polymer may itself be loaded with one or more therapeutic agents or may be applied to delay the release of medicine or otherwise control the rate that the therapeutic agent diffuses into the body.

These and other features of the present invention will become apparent from the following more detailed description, when taken in conjunction with the accompanying drawings which illustrate, by way of example, the principles of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a longitudinal sectional view of a blood vessel with stent manufactured according to one embodiment of the present invention.

FIG. **2** is a porous stent wire or strut in a partially magnified, partially cut away perspective manufactured according to one embodiment of the present invention.

FIG. **3** is a magnified, cross-sectional view of unsintered packed particle.

FIG. **4** is a porous stent wire or strut in partially magnified, partially cut away perspective manufactured according to one embodiment of the present invention.

FIG. **5** is a porous stent wire or strut in partially magnified, partially cut away perspective manufactured according to one embodiment of the present invention.

FIG. **6** is a cross-sectional view of a stent wire or strut manufactured according to one embodiment of the present invention.

FIG. **7** is a cross-sectional view of a stent wire or strut manufactured according to one embodiment of the present invention.

FIG. **8** is a sheet of sintered stent manufactured according to one embodiment of the present invention.

FIG. **9** is a stent formed from a sheet of sintered metal according to one embodiment of the present invention.

FIG. **10** is a cross-sectional, partially cut away view of a sheet of sintered metal manufactured according to the principles of one embodiment of the present invention.

FIG. **11** is a cross-sectional view of a stent wire or strut manufactured according to the principles of one embodiment of the present invention.

FIG. **12** is a cross-sectional view, partially cut away of a sheet of sintered metal manufactured according to the principles of one embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring now to FIG. **1**, the prosthesis of one embodiment is a porous stent **12** that is radially expandable against the walls **14** of a vessel **16**. The stent is loaded with a therapeutic agent in the pores (**18** of FIG. **2**) of the stent. When placed in the vasculature, the therapeutic agent is delivered to the tissue that comes into contact with the stent. The stent of one preferred embodiment is formed of a stent wire that is porous. An example of a porous stent wire is a sintered metal wire. FIG. **2** illustrates a partial microscopic view of a sintered wire that is suitable for use in one embodiment of the present invention. The wire is porous and has several porous cavities **18**. The size of the cavities preferably range between 0.01 and 20 microns in size.

Porous metal is made, according to one preferred embodiment, by the process of sintering metal. Sintering is a process of fabrication where particles are bonded together without entirely melting the particles. Particles are pressed together or molded into a desired shape. A considerable amount of pressure is first applied to press the particles together. Then, the metal is heated to temperatures slightly below the melting point of the metal. Without entirely melting, the particles bond to each other at their respective surfaces. Space remains between the lattice of the particles which define the porous cavities **18**.

The formation of sintered metal is illustrated with reference to FIG. **3** and continued reference to FIG. **2**. FIG. **3** is a microscopic view of a packed lattice **22** of metallic particles **24**. Gaps **26** exist between each particle despite the fact that the particles are pressurized and are in contact with adjacent particles. Particles are preferably sized between 0.02 microns and 20 microns in diameter. Prior to heating, there are no chemical bonds formed between the individual particles. When the metal is heated to slightly below the melting point of the metal, the particles bond with neighboring particles. The gaps in the packed lattice form pores **18** when the particles are sintered. Thus in FIG. **2**, the metal stent wire formed by the process of sintering has porous cavities **18** extending throughout the entire wire, thereby interconnecting the cavities. The cavities then can be filled with a therapeutic agent as hereinafter described. The appropriate pressure and temperature of sintering a particular metal is specific to that particular metal. One skilled in the art of metal fabrication would understand how to sinter any given metal or alloy.

For each of the embodiments, the metal stent material member can be a suitable metal such as stainless steel, tantalum, nickel-titanium alloy, platinum-iridium alloy, molybdenum-rhenium alloy, gold, magnesium, combinations thereof, although other similar materials also may be suitable. The metal can be modified to exhibit different hardnesses, and thus varying stiffnesses, by well known annealing and manufacturing processes.

One of the most important factors to be considered when making a stent according to one embodiment of the present invention is the porosity of the metal. Porosity is the total volume of pores in the sintered metal divided by the total volume of the metal. Porosity determines the amount of a therapeutic agent that can be loaded into a stent of predetermined dimensions. High porosity means that a stent can deliver more therapeutic agents or have a narrower profile because it is less dense. High porosity, according to some embodiments of the present invention, adversely affects the strength and elasticity of a metal. Consequently, there is an ongoing tradeoff between stent strength, on the one hand, and stent profile and stent load capacity on the other hand.

Pore size is a function of particle size and dimension. In one embodiment of the present invention illustrated in FIG. **3**, the particles **24** are generally spherical. Size of the pore **18**, particularly with generally spherical particles, is proportional to particle size. When the particles **24** have inconsistent size, smaller particles tend to fill the gaps between the larger particles. Thus, the porosity of such particles are less predictable. Consistent pore size is also important to ensure that drugs are evenly distributed throughout the stent. Consistent distribution on the other hand ensures that the tissue in contact with the stent will receive an even distribution of a therapeutic agent.

There are several types of drugs that are currently administered at the site that a stent is placed in the vessel. Examples of therapeutic drugs, or agents that can be combined with the polymeric layers include antiplatelets, antifibrin, antithrombin and antiproliferatives. Examples of anticoagulants, antiplatelets antifibrins and antithrombins include but are not limited to sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antibody, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocore). Examples of cytostatic or antiproliferative agents include angiopeptin (a somatostatin analogue from Ibsen), angiotensin converting enzyme inhibitors such as Captopril® (available from Squibb), Cilazapril® (available from Hoffman-LaRoche), or Lisinopril® (available from Merck); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, Lovastatin® (an inhibitor of HMG-COA reductase, a cholesterol lowering drug from Merck), methotrexate, monoclonal antibodies (such as to PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available from Glazo), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic drugs or agents which may be appropriate include alpha-interferon and genetically engineered epithelial cells, for example.

While the foregoing therapeutic agents have been used to prevent or treat restenosis, they are provided by way of example and are not meant to be limiting, since other therapeutic drugs may be developed which are equally applicable for use with the present invention. The treatment of diseases using the above therapeutic agent are known in the art. Furthermore, the calculation of dosages, dosage rates and appropriate duration of treatment are previously known in the art.

The therapeutic agent of one embodiment is preferably in liquid form and is loaded into a stent by immersing the stent in a medicated solution. The therapeutic agent may be dissolved in a solvent or suspended in a liquid mixture. If a suspension of drugs are used, it is important that the pore size of the stent is considerably larger than the therapeutic agent. An average pore size that is more than ten (10) times the particle size of a suspended therapeutic agent is suitable. After the stent is emersed in the medicated solution, the therapeutic agent absorbs into the pores of the stent. At which time, the loaded stent can be removed from the solution and implanted into the vasculature of a patient. Additionally, a therapeutic agent can be loaded into the stent by applying pressure to the fluid to aid the passage of medicated fluid into the porous cavities of the stent. This can be done similar to how fluid can be pressurized through the pores of a filter.

Once loaded, the therapeutic agent remains in place by the surface tension between the walls **28** of the several porous cavities **18** and the therapeutic agent. As shown in FIG. **1**, the loaded or medicated stent **12** is then deployed to the site of arterial closure **13** and is expanded. The expanded stent engages the walls **14** of the vessel **16** to maintain the patency of the vessel. Once in the vessel, the therapeutic agent disseminates from the porous cavities **18**, as depicted in FIG. **2**, of the stent and is absorbed into the tissue of the walls of the vessel that are in contact with the stent.

The advantage of the stent of the present invention over prior art medicated stents is one of profile and strength. Metal, including sintered metal, is stronger than synthetic materials that are capable of being loaded with a therapeutic agent. Thus, in order for a medicated stent to deliver an appropriate amount of a therapeutic agent and structurally maintain vessel patency, the profile of the stent must be substantially larger than metal stents. This is true whether a metal stent is coated with a therapeutic agent, or if the stent is entirely made of a plastic material.

Sintered metal has strength and elasticity that is comparable to regular metal. Sintered metal furthermore has the added feature that it is porous. Consequently, a sintered stent can be made having a profile that is substantially comparable to a conventional metal stent. Yet, a therapeutic agent can be loaded into the pores and delivered to the site of stent implantation without the aid of medicated coatings.

Additionally, many synthetic materials, including materials that are bioabsorbable, cause inflammation of the tissue. A medicated stent that has a therapeutic agent loaded directly into the pores of the stent can avoid synthetic coatings that have been known to cause irritation at the site of stent implantation.

FIG. **4** illustrates an alternative embodiment of a stent wire **30** constructed according to the present invention. The stent is formed of elongated particles **32**, i.e., filaments and fibers. Sintered particles (**24** of FIG. **2**) that are generally spherical in shape are capable of forming sintered metal having a porosity in the range of 0.30 to 0.05. However, when filaments or fibers **32** are sintered, the porosity can be increased above 0.30. The technique of fabricating a stent with elongated filaments or fibers are similar to the method described above for spherical particles or powders. The filaments or fibers are molded and pressurized. Then the fibers are heated to a temperature just below the melting point of the metal.

Greater porosity of a stent made of metal filaments or fibers **32** rather than spherical particles (**24** of FIG. **2**) is obtained because of the irregular shape of the particles. The particles cannot be packed as tightly as regular generally spherical particles. Furthermore, the particles can be packed less densely and still maintain contact between the particles to allow sintering. Thus, the void space or pores **34** in the sintered metal are larger.

The strength of a stent wire **30** using filaments in FIG. **4** is improved because the individual strands have larger surface area to volume and contact a greater number of neighboring strands. Thus, each filament or fiber will have a larger bonding surface and may bond with a greater number of neighboring fibers. A matrix of overlapping filaments or fibers is thus formed with greater porosity and stronger inter-particle bonding.

In yet another embodiment, wire fibers **36** are woven or twined into a structure **38** as illustrated in FIG. **5**. The individual strands cooperate in a synergistic manner to reinforce the strength of the wire. Additionally, the wire fibers can be woven into the form of a sintered metal sheet having improved and reinforced strength or a sintered metal tube. Other combinations of particle size and shape can be employed to form a stent wire having different characteristics.

In another embodiment illustrated in FIG. **6**, the stent wire **42** is formed of an inner core **44** and an outer layer **41** of sintered particles. The outer layer is formed from particles having a different diameter than the diameter of the particles that form the inner core. For example, the core of the metal is formed of particles that have a diameter in the range of 10–20 microns at the core of the wire. Surrounding the core are particles that have a diameter in the range of 2–4 microns on the outer surface. The larger particles create a core having larger pores **52**. This results in higher porosity and thus a higher load capacity. The smaller particles on the outer layer form smaller pores **54** which reduce the rate of diffusion of drugs into the tissue of the vessel.

When a therapeutic agent is loaded into a stent formed of the stent wire **42** illustrated in FIG. **6** a larger volume can be stored in the larger pores **52** at the core **44** of the stent wire. Once the stent is placed into the vessel, the therapeutic agent in the stent wire is delivered at a rate determined by the smaller pores **54** in the outer layer **46** of the stent wire. Such a structure is expected to have a benefit of being able to store a large amount of therapeutic agent at the core and deliver the therapeutic agent at a slower rate. Consequently, this design is desirable for low-dose, long-term drug therapy.

Alternatively, according to another embodiment of the present invention shown in FIG. **7**, a stent wire **56** is formed from sintered particles **58**. The pores **62** formed between the sintered metal particle surrounding the solid core retain the therapeutic agent. The total porosity of a stent having a solid core and porous outer layer is much lower than a stent wire of similar proportion that is entirely made of sintered particles. However, the solid core reinforces the tensile strength and elasticity of the metal stent and is considerably stronger. Thus, it is desirable to use a sintered stent with a solid core for applications where maximum tensile strength and elasticity is desirable and only a relatively small amount of therapeutic agent is needed.

The sintered metal stent of yet another embodiment of the present invention can be made of material formed in different shapes than sintered metal. For example, the stent can be formed of a sheet of sintered metal as shown in FIG. **8** or a sintered metal tube. By way of example, metal particles **66** are arranged and pressurized into a sheet. The sheet is heated to a temperature below the melting point of the particles as described previously. The sheet of sintered metal is porous and has a plurality of pores **68**.

The same principles that apply to porosity and pore size of a wire apply equally to a sintered stent that is formed into a sheet or tube. The advantage of forming the stent from a sheet of metal is that the stent is radially expandable without placing a great deal of strain on the metal lattice when it is expanded. A sheet or tube of sintered metal can be cut in the desired shape to form the metal structural member with a laser, such as a continuous CO_2 laser, a pulsed YAG laser, or an excimer laser, for example, or alternatively, by chemical etching or stamping. When cut from a flat sheet, the stent is then rolled into a cylindrical configuration and laser welded along the longitudinal edges.

The stent can be formed into a particular pattern known in the art for stents formed from metal sheets. One such pattern is a rolled locking design and is illustrated in FIG. **9**. The sheet is etched into a stent configuration that has a head portion **72** that includes one or more slots **74** for receipt of a like number of tail portions **76**. The tail portions are received into the slots so as to form a cylindrical loop. The tail end includes a plurality of teeth **78** adapted to cooperatively engage the slot of the head portion. When the teeth engage the slot, the tail is retained in place in an expanded state. Additionally, holes **80** are formed throughout the stent to reduce the metal to air ratio of the stent. The less metal in contact with the wall **14** of the vessel **16**, the better the blood compatibility of the stent.

Prior to deployment, the tail end is coiled into a retracted position. The tail is threaded through the slot and wound. It is expanded by a balloon according to principles that are well known in the art for delivering and implanting a stent. As the stent is expanded by a balloon during deployment it unwinds and the teeth lock into the slots at a desired radial diameter to prevent the stent from returning to its original retracted state.

A benefit of the coiled stent shown in FIG. **9** is that the stent **70** can be etched to have a minimal surface area that comes in contact with the walls of the vessel. This may be an important feature when it is desired to cover an entire portion of the walls of a blood vessel with a therapeutic agent because the coiled sheet metal stent can be configured to maintain maximum surface area contact with the wall of the blood vessel in contrast to wire stents.

With reference to FIG. **10**, another embodiment of the present invention is a sheet formed of sintered particles that are sintered to both sides **84** and **86** of a metal sheet **82**. The stent of FIG. **10** is similar in structure to the stent wire of FIG. **7** that has a solid core and has porous particles sintered to the core forming a porous outer layer. The solid core reinforces the strength of the metal. The metal sheet also provides a barrier through which a therapeutic agent cannot pass. Thus, a therapeutic agent loaded into the pores **92** on the top side of **84** the sheet permeates in a first direction **88** outward from the solid core. A therapeutic agent loaded into the pores **94** on the bottom side **86** of the solid wire permeates only in a second direction **90** opposite to the direction of the therapeutic agent loaded into the pores on the top side.

When a stent as shown in FIG. **10** is looped into a cylindrical formation and placed into a vessel, only the top side **84**, which is directed radially outward, engages the walls of the vessel. The bottom side **94** faces radially inward and does not come in contact with the walls of the vessel. Thus, if it is desired, a first therapeutic agent can be loaded into the top side to treat the tissue in the wall of the vessel. A second therapeutic agent can be loaded into the bottom side to prevent coagulation of the blood flowing in the vessel. Additionally, the stent can be formed so that particles are sintered only to one side of the stent. A therapeutic agent is loaded into the sintered metal on the porous side of the stent. When a stent is formed from a one-sided porous stent, it can be oriented radially outward to deliver a therapeutic agent to the tissue in the wall of the stent.

FIG. **11** illustrates a cross-sectional view of a stent wire of strut according to one embodiment of the invention. The sheet has a plurality of porous cavities or pores **98**. A therapeutic agent is loaded into the pores of the sintered metal. Then, a coating **100** is applied to the sintered metal. The coating may be used for several purposes as illustrated hereinafter.

With reference to FIG. **12**, another embodiment of the invention is shown wherein the stent is formed of a sintered sheet **104** of metal having core **106** formed of large diameter particles **108** that form large pores. The core layer **106** is sandwiched between two layers **110** and **112** formed of smaller diameter particles **114** or particles that form smaller diameter pores. Such a sheet is formed by orienting a middle or core layer **106** of large diameter particles along a plane. A top layer of smaller diameter particles is arranged in a plane parallel to and above the middle layer. A bottom layer of particles are arranged in a plane parallel to and below the middle layer. The three layers are pressed together and sintered into a single sheet. The sheet can then be cut or etched into a stent configuration.

While one of the benefits of the present invention is to provide a stent that does not require a coating for the purpose of delivering a therapeutic agent to the blood vessel, the application of a coating after a therapeutic agent is loaded into the pores of the sintered metal does not defeat the utility of the present invention. For example, when a therapeutic agent is loaded into the pores of the stent and into a polymeric coating, the profile of the polymeric coating can be reduced. Alternatively, a larger dosage of a therapeutic agent can be delivered to the site of stent implantation. Additional benefits are observed by loading a stent with a therapeutic agent in the pores of the metal and then further applying a coating to the stent. Furthermore, even if a coating is applied to the stent, the principles of reducing profile and reinforcing the stent are still apparent because a greater volume of therapeutic agent can be delivered by a coated sintered stent than a coated, solid stent have comparable dimensions.

The polymeric material that coats a sintered metal stent of the invention preferably comprises a biodegradable, bioabsorbable polymeric film that is capable of being loaded with and capable of releasing therapeutic drugs. The polymeric coatings preferably include, but are not limited to, polycaprolactone (PCL), poly-DL-lactic acid (DL-PLA) and poly-L-lactic acid (L-PLA) or lactide. Other biodegradable, bioabsorbable polymers such as polyorthoesters, polyiminocarbonates, aliphatic polycarbonates, and polyphosphazenes may also be suitable, and other non-degradable polymers capable of carrying and delivering therapeutic drugs may also be suitable. Examples of non-degradable synthetic polymers are polyurethane,

polyethylene, polyethylene teraphthalate, ethylene vinyl acetate, silicone and polyethylene oxide (PEO). The polymeric layers, according to one embodiment is to be loaded with a pharmacologic agent for use in localized drug therapy. As used in this description, the terms biodegradable, bioabsorbable, reabsorbable, degradable, and absorbable are meant to encompass materials that are broken down and gradually absorbed or eliminated by the body, whether these processes are due to hydrolysis, metabolic processes, bulk or surface erosion. In each of the foregoing embodiments, one polymeric layer is preferably about 0.0001 to 0.002 inches thick.

The thin polymeric films used to coat the stent are preferably first intermixed with the drug or drugs to be delivered, and then are typically laminated or solvent cast to the surface of the metal structural member. Lamination processing methods and temperatures can vary widely depending on the polymers used and the temperature sensitivity of the loaded drugs. Alternatively, the metal structure of the stent can be encapsulated in the layers of polymeric material by solvent casting, melt processing, insert molding, and dip coating.

In one embodiment of the present invention, the membrane is bioabsorbable, but no therapeutic agent is loaded into the polymer. The coating **100** dissolves after implantation and this delays the time that a therapeutic agent is released into the vasculature of a patient. The thickness of the coating as well as the rate at which the coating is bioabsorbed determines the length of time that the stent is mounted into the vascular before a therapeutic agent is delivered from the pores of the stent. Additionally, a therapeutic agent can be loaded into the bioabsorbable coating. Thus a therapeutic agent will be delivered to the stent at a rate determined by the bioabsorbability of the coating. Once the bioabsorbable material has completely dissolved, the therapeutic agent in the pores can be delivered at a rate determined by the pore size and porosity.

In another embodiment, it is preferred that the coating **100** is permeable and non-absorbable. In such circumstances, the rate at which the drugs permeate into the tissue is controlled by the physical properties of the particular coating selected. Additionally, the coating may be selected to reduce restenosis, thrombosis or other tissue inflammation. For example, a heparin coating is known in the art to reduce blood clotting. Heparin, when coated on a stent reduces clotting of blood on the surface of the stent. The heparin coating is affixed to the-surface of the stent through ionic bonding, end point attaching, or photo-linking the heparin.

In yet another embodiment, a first therapeutic agent is loaded into the coating and a second therapeutic agent is loaded into the pores of the stent. This may be the case when a series of drug dosages or concentrations are needed. When such a stent is placed into the vasculature, the first therapeutic agent is absorbed first by the stent and a second therapeutic agent is absorbed later by the vasculature. This variation adds a further dimension to drug treatment allowing for sequential drug therapy at the site of placement of a stent.

It will be apparent from the foregoing that while particular forms of the invention have been illustrated and described, various modifications can be made without departing from the spirit and scope of the invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

What is claimed is:

1. A method of manufacturing a stent for providing local delivery of a therapeutic agent at an implantation site, comprising:

sintering metallic fibers into a sintered stent material having a plurality of porous holding cavities open to one side;

forming the sintered stent material into a stent; and

loading a therapeutic agent into the cavities of the stent prior to implanting the stent at the implantation site.

2. The method of claim **1**, wherein said plurality of porous holding cavities extend throughout the sintered stent material.

3. The method of claim **1**, futher comprising the step of weaving said metallic fibers prior to sintering the metallic fibers to form said sintered stent material.

4. The method of claim **1**, wherein:

the sintered stent material comprises a sheet; and

the forming step includes chemical etching the sheet into the form of an expandable stent.

5. The method of claim **2**, wherein the metallic fibers are woven into a sheet prior to said sintering step.

6. The method of claim **1**, wherein:

the sintered stent material comprises a sheet; and

the forming step includes cutting the sheet with a laser into the form of a stent.

7. The method of claim **5**, wherein the metallic fibers are woven into a sheet prior to said sintering step.

8. The method of claim **1**, wherein said sintered stent material comprises a porous metal wire.

9. The method of claim **1**, further comprising the step of weaving the metallic fibers into a sheet.

10. The method of claim **2**, wherein the stent is emersed for a period of time sufficient to permit a therapeutic agent to be absorbed into the porous cavities of the stent.

11. The method of claim **2**, wherein the stent is emersed for a period of time sufficient to permit a therapeutic agent to be absorbed into the porous cavities of the stent.

12. The method of claim **2**, wherein the therapeutic agent is an anti-fibrin agent.

13. The method of claim **2**, wherein the therapeutic agent is an antithrombin agent.

14. The method of claim **2**, wherein the therapeutic agent is an anti-proliferative agent.

15. The method of claim **2**, wherein the therapeutic agent is an anti-coagulant.

16. The method of claim **2**, wherein the therapeutic agent is a $GPII_6III_a$ blocker.

17. The method of claim **2**, wherein the therapeutic agent is selected from the group consisting of forskolin, aspirin, dipyridamole, coumadin, ticlopodine, and heparin.

18. The method of claim **2**, wherein the therapeutic agent is a vaso-active drug.

19. The method of claim **2**, wherein the therapeutic agent is an anti-inflammatory agent.

20. The method of claim **2**, wherein the therapeutic agent promotes endothelialization.

21. The method of claim **2**, further comprising coating the stent with a polymer.

22. The method of claim **21**, wherein the coating step occurs after the loading step.

23. The method of claim **21**, wherein the polymer is configured to release the therapeutic agent at a substantially constant rate.

24. The method of claim **21**, wherein the polymer is a biopolymer.

25. The method of claim **21**, wherein the polymer is a poly lactic acid or fibrin.

26. The method of claim **25**, wherein the polymer is selected from the group consisting of polyurethane, poly-

ethylene teraphthalate tetrafluoride, polyethylene, polyethylene oxide (PEO) and silicone.

27. The method of claim **21**, wherein the polymer is a synthetic polymer.

28. The method of claim **27**, wherein the polymer is a hydrogel.

29. The method of claim **21**, wherein the polymer is a heparin coating.

30. The method of claim **21**, wherein the polymer is mixed with the therapeutic agent.

31. The method of claim **21**, wherein the polymer is degradable.

32. The method of claim **1**, wherein the cavities are open on their respective one ends and the sintered stent material forms closure walls on the respective opposite ends.

33. The method of claim **1**, wherein said sintered stent material forms respective cavity side walls to define the respective holding cavities, and such side walls cause such cavities to cooperate with the loaded therapeutic agent in providing surface tension for holding the therapeutic agent in the respective cavities.

34. The method of claim **1**, wherein said sintered stent material comprises a plurality of layers with at least one layer configured with the cavities opening outwardly to the one side and second layer forming a closure wall closing the respective cavities from opening to the opposite side.

35. The method of claim **1**, wherein said sintered stent material comprises a pair of coextensive outer layers formed with the cavities facing outwardly in opposite directions and an intermediate layer sandwiched between the outer layers.

36. The method of claim **1**, wherein the cavities are of substantially uniform size.

37. The method of claim **1**, wherein the cavities are of substantially irregular size.

38. The method of claim **1**, wherein said sintered stent material comprises a single layer.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,240,616 B1
DATED : June 5, 2001
INVENTOR(S) : John Y. Yan

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,

Item [56], U.S. PATENT DOCUMENTS, add the following:

--	4,355,462	10/1982	MacGregor
	5,571,187	11/1996	Derarathan
	5,725,567	3/1998	Wolff, et al. --.

Column 10,

Line 17, change "**2**", to read -- **4** --.

Line 24, change "**5**", to read -- **6** --.

Lines 30-32, delete entire claim "10", and replace with the following:

-- **10.** The method of claim **2**, wherein the step of loading the therapeutic agent comprises immersing the stent in a liquid solution containing the therapeutic agent. --.

Line 64, change "**21**", to read -- **24** --.

Signed and Sealed this

Twenty-sixth Day of November, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,240,616 B1
DATED : June 5, 2001
INVENTOR(S) : John Y. Yan

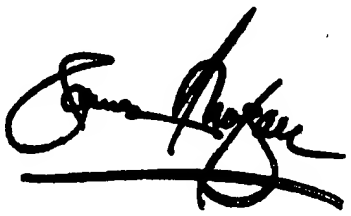
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2,
Line 39, change "emersed" to -- immersed. --

Column 10,
Line 32, change "emersed" to -- immersed. --

Signed and Sealed this

Eleventh Day of February, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US006261320B1

(12) **United States Patent**
Tam et al.

(10) **Patent No.: US 6,261,320 B1**
(45) **Date of Patent: Jul. 17, 2001**

(54) **RADIOACTIVE VASCULAR LINER**

(75) Inventors: **Lisa A. Tam**, Lake Forest; **Brett A. Trauthen**, Newport Beach, both of CA (US)

(73) Assignee: **Radiance Medical Systems, Inc.**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/253,177**

(22) Filed: **Feb. 19, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/975,584, filed on Nov. 21, 1997, now Pat. No. 6,120,535, which is a continuation-in-part of application No. 08/881,956, filed on Jun. 25, 1997, now Pat. No. 6,090,136, which is a continuation-in-part of application No. 08/754,816, filed on Nov. 21, 1996, now Pat. No. 5,728,150.

(51) **Int. Cl.**[7] **A61F 2/00**

(52) **U.S. Cl.** **623/1.15**; 623/1.4; 623/1.39

(58) **Field of Search** 623/1.15, 1.2, 623/1.36, 1.39, 1.4

(56) **References Cited**

U.S. PATENT DOCUMENTS

Re. 34,327	7/1993	Kreamer .
3,324,847	6/1967	Zoumboulis .
4,115,536	9/1978	Rothman et al. .
4,124,705	11/1978	Rothman et al. .
4,126,669	11/1978	Rothman et al. .
4,225,790	9/1980	Parsons, Jr. et al. .
4,323,055	4/1982	Kubiatowicz .
4,423,725	1/1984	Baran et al. .
4,581,017	4/1986	Sahota .
4,588,395	5/1986	Lemelson .
4,655,771	4/1987	Wallsten .
4,665,918	5/1987	Garza et al. .
4,674,480	6/1987	Lemelson .
4,706,652	11/1987	Horowitz .
4,739,762	4/1988	Palmaz .
4,740,207	4/1988	Kreamer .
4,762,129	8/1988	Bonzel .
4,776,337	10/1988	Palmaz .
4,800,882	1/1989	Gianturco .
4,815,449	3/1989	Horowitz .
4,819,618	4/1989	Liprie .
4,877,030	10/1989	Beck et al. .
4,878,492	11/1989	Sinofsky et al. .
4,922,905	5/1990	Strecker .
5,007,926	4/1991	Derbyhire .
5,011,677	4/1991	Day et al. .
5,019,369	5/1991	Presant et al. .
5,040,548	8/1991	Yock .
5,059,166	10/1991	Fischell et al. .
5,059,211	10/1991	Stack et al. .

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

0 433 011 B1	7/1994	(EP) .
0 688 580 A1	12/1995	(EP) .
0 593 136 B1	3/1997	(EP) .

(List continued on next page.)

OTHER PUBLICATIONS

Radiation Quantities and Units, ICRU Report 33, International Commisson on Radiation, Units and Measurements, Apr. 15, 1980.

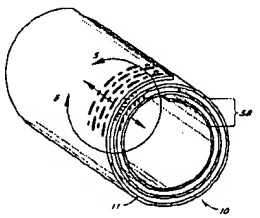
(List continued on next page.)

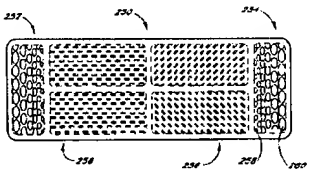
Primary Examiner—Michael J. Milano
(74) *Attorney, Agent, or Firm*—Knobbe, Martens, Olson & Bear LLP

(57) **ABSTRACT**

Disclosed is a radioactive tubular prosthesis formed by rolling a flexible sheet around a longitudinal axis. Preferably, the prosthesis is self expandable under the radially outwardly directed spring bias of the rolled sheet. At least a portion of the sheet is provided with a coating comprising at least one radioisotope.

11 Claims, 10 Drawing Sheets





U.S. PATENT DOCUMENTS

5,061,273	10/1991	Yock .
5,078,726	1/1992	Kreamer .
5,089,006	2/1992	Stiles .
5,100,429	3/1992	Sinofsky et al. .
5,106,360	4/1992	Ishiwara et al. .
5,167,614	12/1992	Tessmann et al. .
5,171,262	12/1992	MacGregor .
5,176,617	1/1993	Fischell et al. .
5,192,307	3/1993	Wall .
5,199,939	4/1993	Dake et al. .
5,213,561	5/1993	Weinstein et al. .
5,234,448	8/1993	Wholey et al. .
5,242,399	9/1993	Lau et al. .
5,254,127	10/1993	Wholey et al. .
5,266,073	11/1993	Wall .
5,267,960	12/1993	Hayman et al. .
5,302,168	4/1994	Hess .
5,302,369	4/1994	Day et al. .
5,306,286	4/1994	Stack et al. .
5,306,294	4/1994	Winston et al. .
5,344,426	9/1994	Lau et al. .
5,354,257	10/1994	Roubin et al. .
5,354,309	10/1994	Schnepp-Pesch et al. .
5,366,473	11/1994	Winston et al. .
5,383,926	1/1995	Lock et al. .
5,405,379	4/1995	Lane .
5,411,466	5/1995	Hess .
5,411,549	5/1995	Peters .
5,411,551	5/1995	Winston et al. .
5,423,885	6/1995	Williams .
5,424,288	6/1995	Order .
5,441,515	8/1995	Khosravi et al. .
5,443,500	8/1995	Sigwart .
5,449,382	9/1995	Dayton .
5,484,384	1/1996	Fearnot .
5,498,227	3/1996	Mawad .
5,503,613	4/1996	Weinberger .
5,540,659	7/1996	Tierstein .
5,540,713	7/1996	Schnepp-Pesch et al. .
5,605,530	2/1997	Fischell et al. .
5,616,114	4/1997	Thornton et al. .
5,618,266	4/1997	Liprie .
5,643,171	7/1997	Bradshaw et al. .
5,653,683	8/1997	D'Andrea .
5,662,580	9/1997	Bradshaw et al. .
5,674,177	10/1997	Hehrlein et al. .
5,683,345	11/1997	Waksman et al. .
5,688,220	11/1997	Verin et al. .
5,707,332	1/1998	Weinberger .
5,713,828	2/1998	Coniglione .
5,720,717	2/1998	D'Andera .
5,722,984	3/1998	Fischell et al. .
5,723,003	3/1998	Winston et al. .
5,728,042	3/1998	Schwager .
5,728,150	3/1998	McDonald et al. .
5,730,698	3/1998	Fischell et al. .
5,755,690	5/1998	Saab .
5,762,631	6/1998	Klein .
5,782,740	7/1998	Schneiderman .
5,782,741	7/1998	Bradshaw et al. .
5,782,742	7/1998	Crocker et al. .
5,795,286	8/1998	Fischell et al. .
5,860,991	1/1999	Klein et al. .
5,863,284	1/1999	Klein .
5,871,436	2/1999	Eury .
5,879,282	3/1999	Fischell et al. .
6,013,019	1/2000	Fischell et al. .
6,019,718	2/2000	Hektner .
6,024,690	2/2000	Lee et al. .
6,033,357	3/2000	Ciezki et al. .
6,042,600	3/2000	Rosenthal et al. .
6,050,930	4/2000	Teirstein .
6,059,713	5/2000	Urick et al. .
6,059,714	5/2000	Armini et al. .
6,059,752	5/2000	Segal .

FOREIGN PATENT DOCUMENTS

WO 93/04735	3/1993	(WO) .
WO 94/23789	10/1994	(WO) .
WO 94/26205	11/1994	(WO) .
WO 95/19807	7/1995	(WO) .
WO 95/29008	11/1995	(WO) .
WO 96/10436	4/1996	(WO) .
WO 96/13303	5/1996	(WO) .
WO 96/14898	5/1996	(WO) .
WO 96/22121	7/1996	(WO) .
WO 97/18012	5/1997	(WO) .

OTHER PUBLICATIONS

Scanning Electron Microscopy Evaluation of Porous and Nonporous Arterial Substitutes, Giovanni B. Ratto, M.D., Carmen Lunghi, M.D., Enzo Spinelli, M.D., Riccardo Agati, M.D., Marzia Tomellini, M.D., and Giovanni Motta, M.D., Genoa, Italy, Surgery, Gynecology & Obstetrics, Sep. 1982, vol. 155.

Morphology of Healing in Vascular Prosthesis, G. Rahlf, P. Urban, and R.M. Bohle, Read at the 14th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery, Bad Nauheim 1985, Thoracic Cardiovascular Surgeon 34 (1986).

Endothelial Cell Adhesion to Vascular Prosthetic Surfaces, D. Gourevitch, Carolyn E. Jones, J. Crocker and M. Goldman, Presented at Biointeractions '87, Cambridge, UK in Jul. 1987, Biomaterials 1988, vol. 9, Jan.

Restenosis After Ballon Angioplasty, A Practical Proliferative Model in Porcine Coronary Arteries, Robert S. Schwartz, MD, Joseph G. Murphy, MB, William D. Edwards, MD. Allan R. Camrud, RN, Ronald E. Vlietstra, MB, BCh, and David R. Holmes, MD, Circulation, vol. 82, No. 6, Dec. 1990.

Effects of high–dose intracoronary irradiation on vasomotor function and smooth muscle histopathology, Joseph G. Wiederman, Jeffery A. Leavy, Howard Armols, Allan Schwartz, Shunichi Homma, Charles Marboe and Judah Weinberger, Interventional Cardiology Center, Department of Medicine and Radiation Oncology and Section of Cardiac Pathology, Columbia–Presbyterian Medical Center and Columbia University, 1994 the American Physiological Society.

Intracoronary Irratiation Markedly Reduces Restenosis Restenosis After Ballon Angioplasty in a Procine Model, Joseph G. Wiedermann, MD, Charles Marboe, MD, Howard Amols, PhD, Allan Schwartz, MD, FACC, Judah Weinberger, MD, PhD, FACC, JACC, vol. 23. No. 6, May 1994:1491–8.

Intracoronary Irradiation Markedly Reduces Neointimal Proliferation After Balloon Angioplasty in a Swine: Persistant Benefit at 6–Month Follow–up, Joseph G. Wiedermann, MD, Charles Marboe, MD, Howard Amols, PhD, Allan Schwartz, MD, FACC, Judah Weinberger, MD, PhD, FACC, JACC, vol. 25. No. 6, May 1995:1451–6.

Discoveries in Radiation for Restenosis, Emory University of School of Medicine, Presented by The Andreas Gruentzig Cardiovascular Center and the Department of Radiation Oncology of Emory University School of Medicine; J.W. Marriott Hotel at Lenox, Atlanta, GA, Jan. 11–12, 1996.

Radioactive Balloon Catheter to Inhibit Restenosis after Angioplasty.

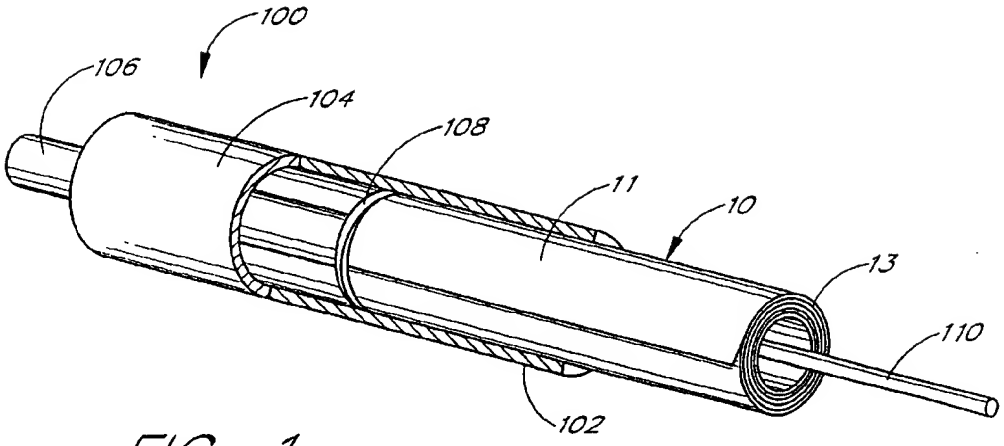


FIG. 1

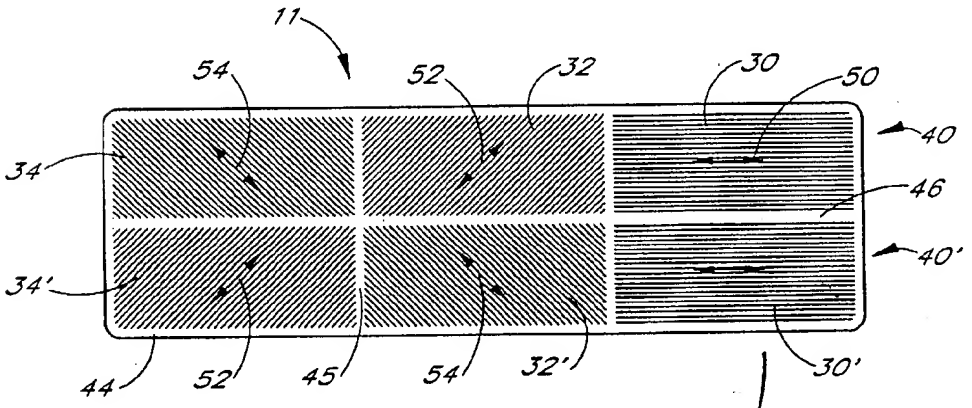


FIG. 2

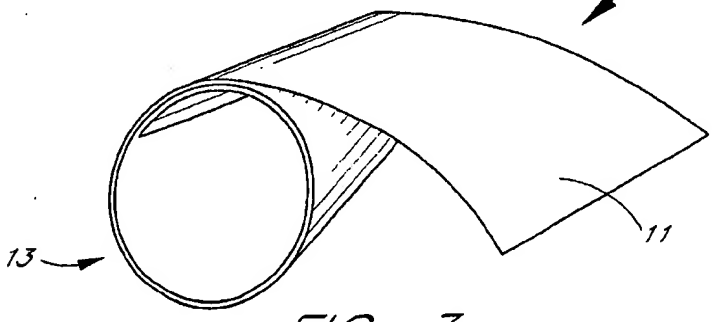


FIG. 3

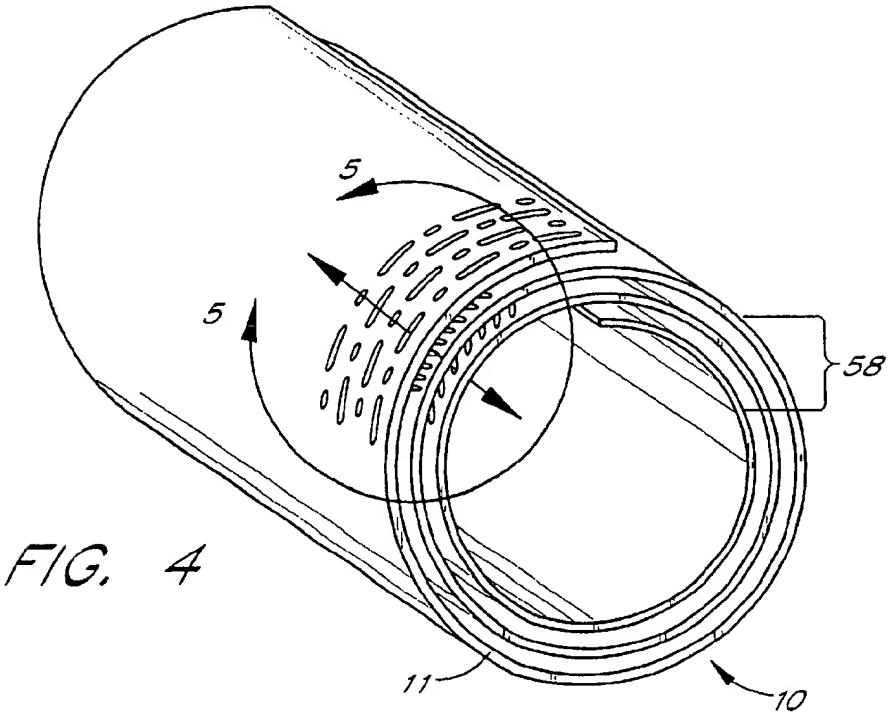


FIG. 4

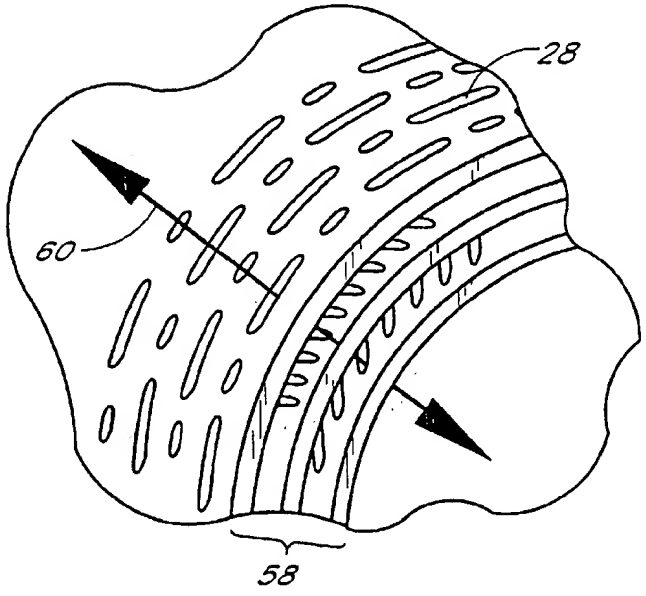


FIG. 5

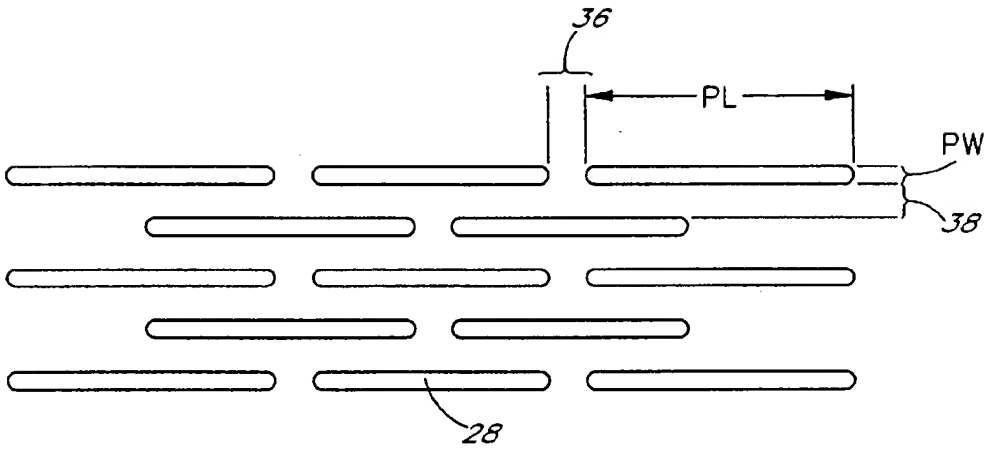


FIG. 6

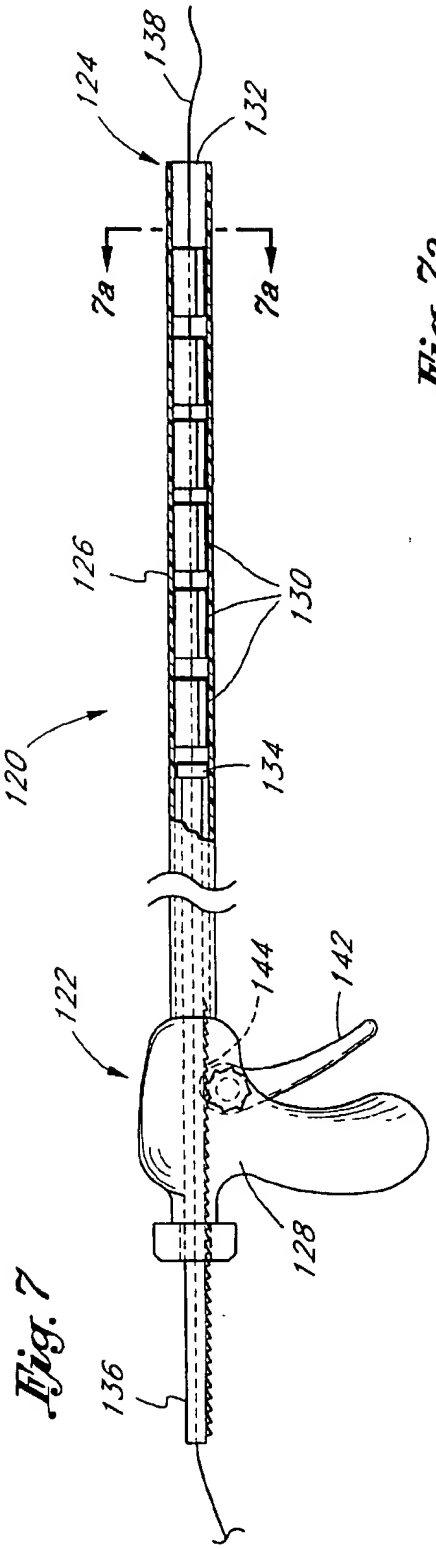


Fig. 7

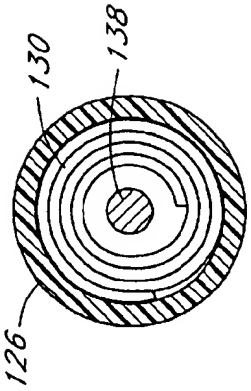


Fig. 7a

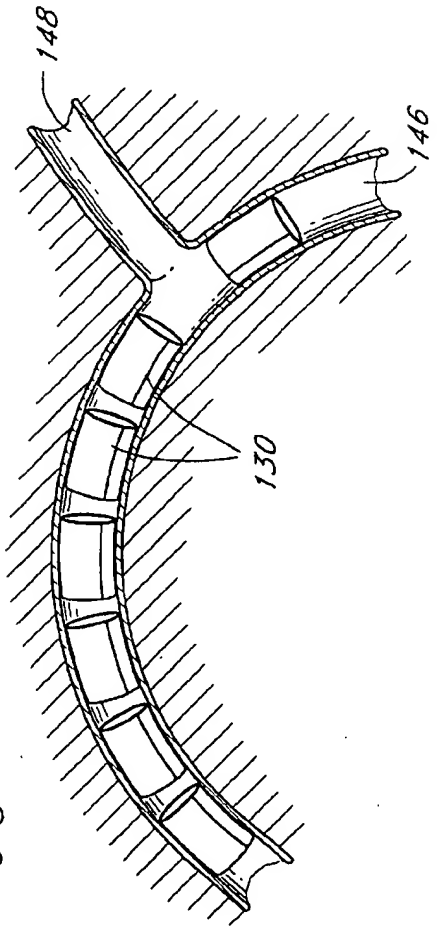


Fig. 8

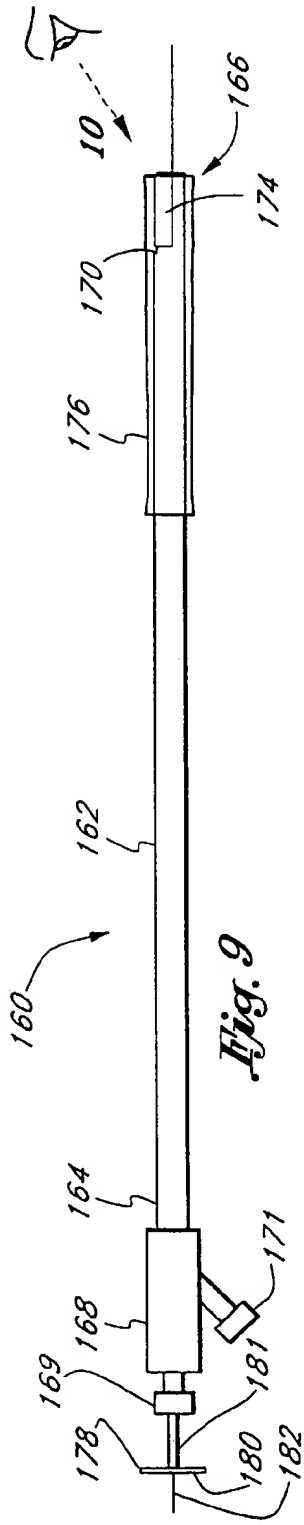


Fig. 9

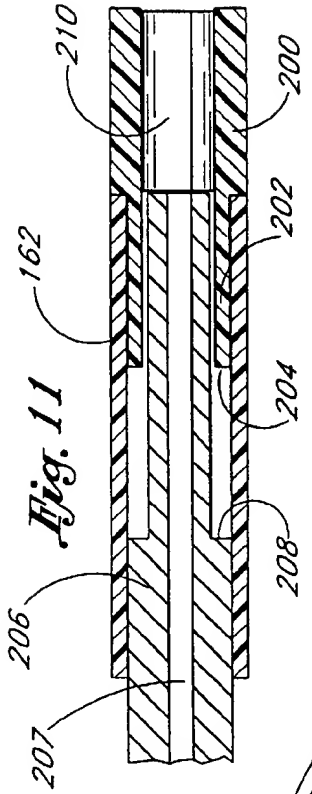


Fig. 11

Fig. 10

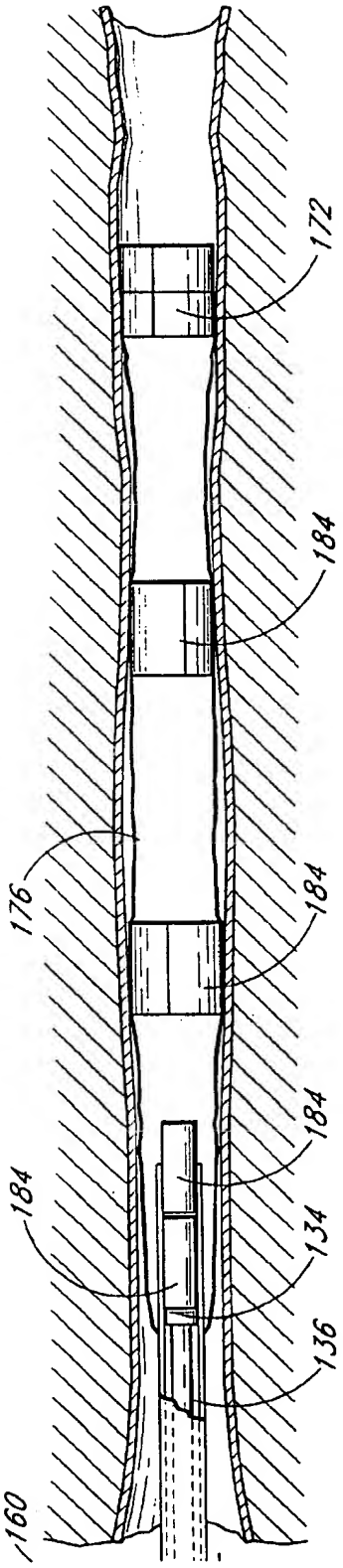


Fig. 12

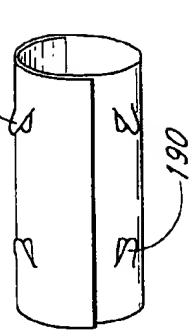


Fig. 14

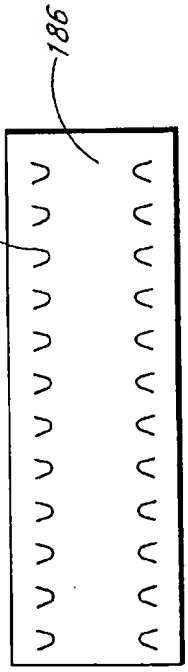


Fig. 13

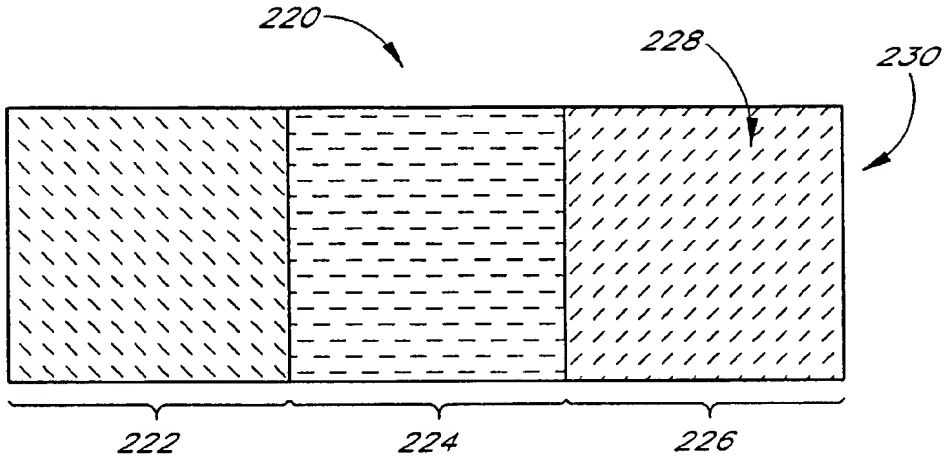


FIG. 15

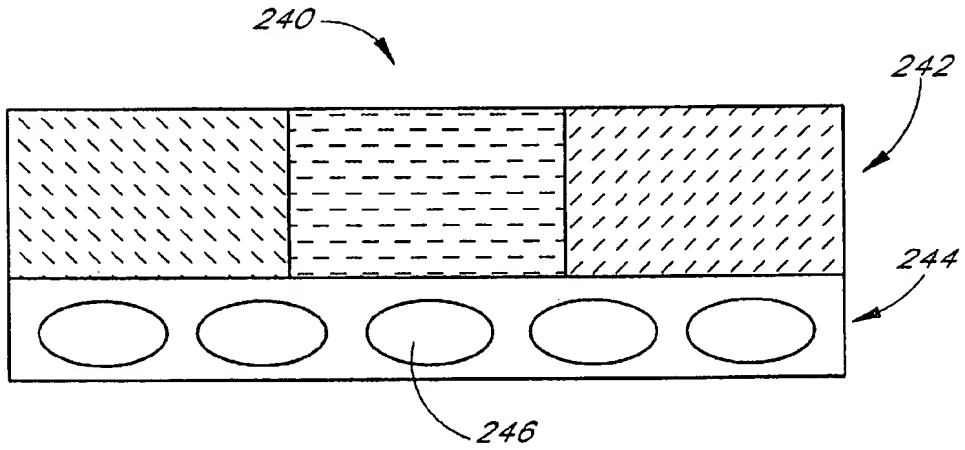


FIG. 16

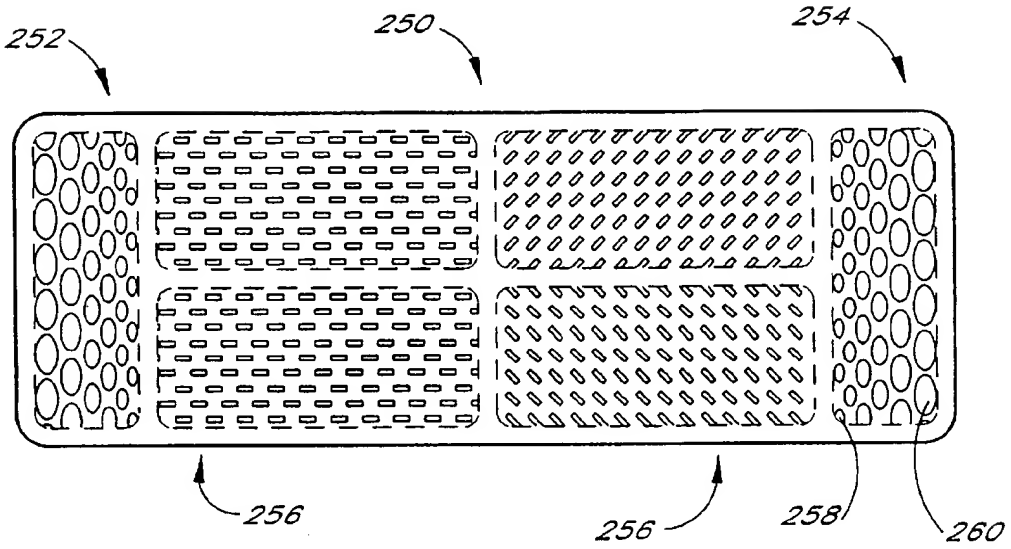


FIG. 17

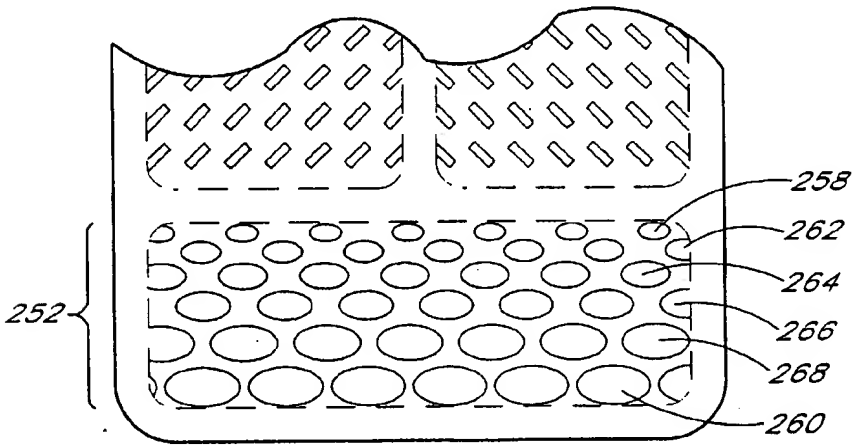


FIG. 18

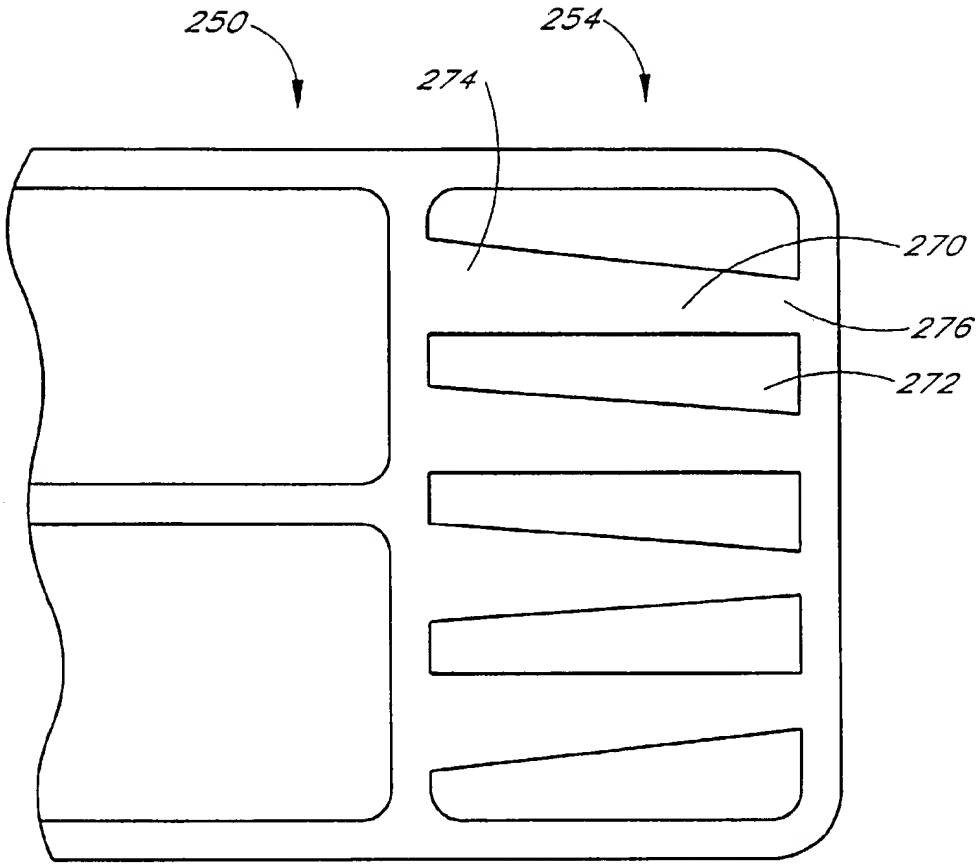


FIG. 19

FIG. 20A

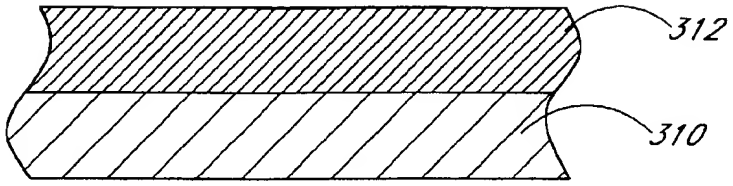


FIG. 20B

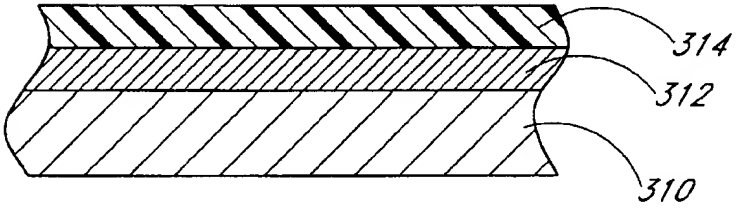


FIG. 20C

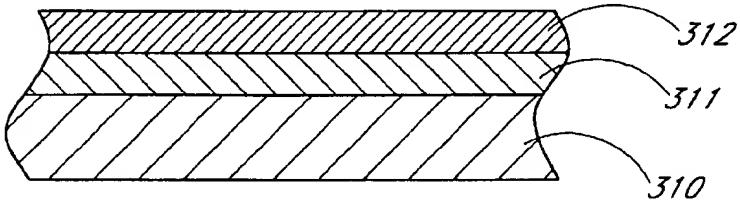
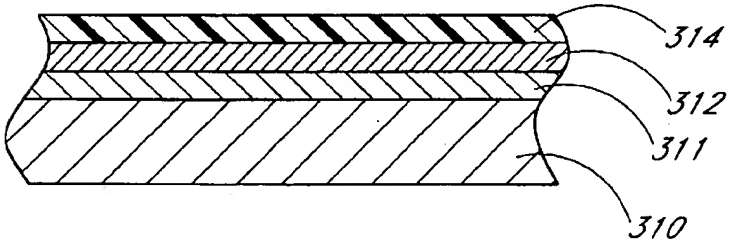


FIG. 20D



RADIOACTIVE VASCULAR LINER

CROSS-REFERENCE TO RELATED APPLICATION

This is a continuation-in-part of commonly assigned, U.S. patent application Ser. No. 08/975,584 filed Nov. 21, 1997, now U.S. Pat. No. 6,120,535, which is a continuation-in-part of U.S. patent application Ser. No. 08/881,956 filed Jun. 25, 1997, now U.S. Pat. No. 6,090,136, which is a continuation-in-part of U.S. patent application Ser. No. 08/754,816 filed Nov. 21, 1996, now U.S. Pat. No. 5,728,150.

FIELD OF THE INVENTION

The present invention relates to coated or covered intraluminal stents and grafts that are adapted to be advanced in a collapsed roll to the site of an aneurysm, defect or injury of a body vessel and expanded or allowed to self expand across the site, wherein said coating or covering comprises at least one radioisotope.

BACKGROUND OF THE INVENTION

PTA treatment of the coronary arteries, percutaneous transluminal coronary angioplasty (PTCA), also known as balloon angioplasty, is the predominant treatment for coronary vessel stenosis. Approximately 300,000 procedures were performed in the United States in 1990 and nearly one million procedures worldwide in 1997. The U.S. market constitutes roughly half of the total market for this procedure. The increasing popularity of the PTCA procedure is attributable to its relatively high success rate, and its minimal invasiveness compared with coronary by-pass surgery. Patients treated by PTCA, however, suffer from a high incidence of restenosis, with about 35% or more of all patients requiring repeat PTCA procedures or by-pass surgery, with attendant high cost and added patient risk.

More recent attempts to prevent restenosis by use of drugs, mechanical devices, and other experimental procedures have had limited long term success. Stents, for example, dramatically reduce acute reclosure, and slow the clinical effects of smooth muscle cell proliferation by enlarging the minimum luminal diameter, but otherwise do nothing to prevent the proliferative response to the angioplasty induced injury.

Restenosis is now believed to occur at least in part as a result of injury to the arterial wall during the lumen opening angioplasty procedure. In some patients, the injury initiates a repair response that is characterized by hyperplastic growth of the vascular smooth muscle cells in the region traumatized by the angioplasty. Intimal hyperplasia or smooth muscle cell proliferation narrows the lumen that was opened by the angioplasty, regardless of the presence of a stent, thereby necessitating a repeat PTCA or other procedure to alleviate the restenosis.

Preliminary studies indicate that intravascular radiotherapy (IVRT) has promise in the prevention or long-term control of restenosis following angioplasty. IVRT may also be used to prevent or delay stenosis following cardiovascular graft procedures or other trauma to the vessel wall. Proper control of the radiation dosage, however, appears to be important to inhibit or arrest hyperplasia without causing excessive damage to healthy tissue. Overdosing of a section of blood vessel can cause arterial necrosis, inflammation, hemorrhaging, and other risks discussed below. Underdosing will result in inadequate inhibition of smooth muscle cell hyperplasia, or even exacerbation of hyperplasia and resulting restenosis.

U.S. Pat. No. 5,059,166 to Fischell discloses an IVRT method that relies on a radioactive stent that is permanently implanted in the blood vessel after completion of the lumen opening procedure. Radiation delivery systems provided on a stent have also been disclosed in U.S. Pat. No. 5,176,617 to Fischell et al., and in U.S. Pat. No. 5,674,177 to Heirlein et al. The use of a stent as a platform is of particular interest because it has been shown to be effective in animals, even at activity ranges as low as 0.14–0.23 μCi (microcuries). Refer, for example, to Fischell, et al., ALow-Dose, β-Particle Emission From Stent Wire Results in Complete, Localized Inhibition of Smooth Muscle Cell Proliferation", *Circulation*, vol. 90, pp. 2956–2963, (1994); Laird et al, AInhibition of Neointimal Proliferation with Low-Dose Irradiation From a β-Particle-Emitting Stent", *Circulation*, 93:529–536 (1996); Carter, et al, AEffects of Endovascular Radiation From a β-Particle Emitting Stent in a Porcine Coronary Restenosis Model [A Dose-Response Study]@, *Circulation* 92:1570–1575 (1995); and Hehrlein, et al, APure β-Particle-Emitting Stents Inhibit Neointima Formation in Rabbits", *Circulation* 93:641–645 (1996).

Several limitations exist in the systems disclosed in the literature and in the currently available art. One limitation is that the isotope chosen for the radiation is dependent on the materials used for the stent. For example, in the systems described in Fischell '617 and '166, Hehrlein '177, and in the stents used in the experiments described by Fischell and Hehrlein in their 1995 papers cited above, the active isotopes were limited to species created by direct neutron activation of the stent in a reactor. This process limits control over the type and amount of radiation that the stent can possess. Hehrlein '177 discloses no less than nine different isotopes created by this process, each with its own half-life, activity level, and radiation characteristics. This set up makes control over the radiation dose extremely difficult, and investigation into the interaction of the radiation with tissue very problematic.

To overcome this limitation, the stents used in the study described by Laird were made by first ion implanting the stent with phosphorous-31 (P-31 or ^{31}P), then placing the stents in a reactor to convert the stable P-31 to the beta-emitting P-32. Alternatively, the radioactive stent described in Fischell '166 and '617 describe coating or otherwise encapsulating a cold version of the target isotope in the stent material, and then placing the stent in a reactor to convert the stable isotope to a radioactive one. This approach, while offering some improvement over the prior method, is limited in the total activity attainable. For example, consider the activation of P-32 by neutron bombardment. Only about 1 in every 100,000 P-31 ions is converted to P-32 in the reactor chamber over a 10-day period. While this conversion rate can be increased, there is a physical limitation to this process dictated by the reactor flux, the cross section of the target atom, and the half-life of the isotope. Moreover, this method does not completely eliminate the activation of non-desired isotopes created from the stent material.

A second limitation relates to the geometry of the prior art radioactive stents. In general, balloon expandable stents comprise a plurality of struts which are spaced apart from each other when the stent is in the expanded state. A radioactive coating or ion implantation into such stents produces a radiation grid pattern which inherently delivers a nonuniform dose of radiation to the vessel wall. Many self expanding stent configurations also produce a nonuniform delivery profile.

Thus, there remains a need for a radioactive vascular liner such as a stent which is capable of delivering a substantially unifonn dose of radiation throughout its delivery zone.

SUMMARY OF THE INVENTION

There is provided in accordance with one aspect of the present invention, a tubular vascular liner for delivering a dose of radiation to the wall of a vessel. The liner comprises a flexible sheet, rolled into a tube having a first diameter for positioning at a site in a vessel. The sheet is unrollable to second, larger diameter for positioning against the wall of the vessel. A radioactive isotope is attached to the sheet, such that the radioisotope is positioned adjacent the vessel wall when the sheet is implanted and enlarged to the second diameter.

Preferably, the sheet is self expandable from the first diameter to the second diameter. In one embodiment, an outer protective coating is provided to minimize the escape of radioisotope from the sheet.

In accordance with another aspect of the present invention, there is provided a radioactive tubular prosthesis. The prosthesis comprises a flexible sheet having a first edge and a second edge. The sheet is rollable into a tube such that the first edge is disposed on the inside of the tube and the second edge is disposed on the outside of the tube. A first transition zone is provided near the first edge, and a second transition zone is provided near the second edge. The first transition zone has an increasing flexibility in the direction of the first edge, and the second transition zone has an increasing flexibility in the direction of the second edge. At least a portion of the sheet is provided with a radioactive coating.

In accordance with another aspect of the present invention there is provided a self expandable radioactive tubular prosthesis. The prosthesis comprises a flexible perforated sheet rolled a first number of revolutions about an axis into a first, insertion diameter. The prosthesis is radially expandable under its own bias by unrolling to a substantially cylindrical prosthesis having a second, implanted diameter with a second, smaller number of revolutions. A sufficient number of perforations through adjacent layers of the sheet align to produce a plurality of ports extending all the way through the side wall of the prosthesis. Preferably, the sheet is provided with zones of differing spring strengths so that an innermost revolution of the sheet conforms substantially to the wall of the cylinder. At least a portion of the sheet is provided with a radioactive coating.

In accordance with a further aspect of the present invention, there is provided a tubular radioactive prosthesis. The prosthesis comprises a flexible sheet, having a longitudinal axis and at least first, second and third groups of apertures extending therethrough. The first group of apertures comprises a first plurality of parallel slots inclined at a first angle with respect to the longitudinal axis. The second group comprises a second plurality of parallel slots inclined at a second angle with respect to the longitudinal axis. The first, second and third groups of apertures are arranged on the sheet such that when the sheet is wrapped about an axis through at least about three revolutions to form a tubular prosthesis, at least some apertures from the first, second and third groups align to produce a plurality of ports extending through the side wall of the prosthesis. A radioactive coating is provided on at least a portion of the sheet.

These and other advantages and features of the invention will become apparent from the following detailed description of the preferred embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a fragmentary perspective view of a vascular liner in accordance with the present invention and the distal end of one exemplary form of a placement system for placing the vascular liner in its collapsed roll state at a desired site in a body lumen;

FIG. **2** is a plan view of one sheet pattern from which the vascular liner of the present invention is formed showing the symmetrical orientation of a pair of first, second and third zones of the sheet containing elongated perforations orientated at complementary angles to one another;

FIG. **3** is a schematic illustration of the sheet of FIG. **2** being rolled into a tubular prosthesis;

FIG. **4** is an enlarged perspective view of the sheet of FIG. **2** rolled up in a tubular body to form overlapping layers having overlapping zones of perforations;

FIG. **5** is a fragmentary enlarged perspective view of a side wall section of three layers of the sheet of FIG. **2** rolled up to overlie one another and depicting alignment of the perforations in the first, second and third perforation zones to provide spaced apart, continuous openings through the side wall; and

FIG. **6** is an enlargement of a portion of the sheet of FIG. **2**, illustrating slot dimensions in accordance with one embodiment of the invention.

FIG. **7** is a side elevational schematic illustration of a multiple vascular liner deployment tool in accordance with another aspect of the present invention.

FIG. *7a* is a cross-sectional view through the line *7a*—*7a* in FIG. **7**.

FIG. **8** is a schematic view of a plurality of vascular liners of the present invention implanted within a curved vessel.

FIG. **9** is a side elevational schematic view of a vascular liner graft deployment tool in accordance with another aspect of the present invention.

FIG. **10** is a perspective view of a distal portion of the deployment tool of FIG. **9**.

FIG. **11** is a cross-sectional view through the distal end of an alternate vascular liner graft deployment tool.

FIG. **12** is a cross-sectional schematic view showing a plurality of tubular supports being positioned within a graft in a body vessel.

FIG. **13** illustrates an unrolled tubular support of the present invention having a plurality of proximal and distal anchors thereon.

FIG. **14** is a perspective view of the sheet of FIG. **13** rolled into the form of a tubular support.

FIG. **15** is a schematic view of an unrolled sheet for construction into a tubular prosthesis.

FIG. **16** is a schematic view of an alternate embodiment of an unrolled sheet.

FIG. **17** is a schematic illustration of a sheet in accordance with the present invention having modified terminal ends.

FIG. **18** is an enlargement of one of the terminal ends of the sheet illustrated in FIG. **17**.

FIG. **19** is an alternate embodiment of a modified sheet end.

FIG. **20A** is a schematic of a cross-section of one embodiment of the vascular liner of the present invention having a radioactive coating thereon comprising a substrate layer, formed by the vascular liner and an isotope layer.

FIG. **20B** is a schematic of a cross-section of another embodiment of a radioactive-coated vascular liner of the present invention, wherein the coating has a substrate layer formed by the vascular liner, an isotope layer and a coating layer.

FIG. **20C** is a schematic of a cross-section of another embodiment of a radioactive-coated vascular liner of the present invention, wherein the coating has a tie layer formed by the vascular liner disposed between the substrate layer and the isotope layer.

FIG. **20D** is a schematic of a cross-section of another embodiment of a radioactive-coated vascular liner of the present invention, wherein the coating has a substrate layer formed by the vascular liner, a tie layer, an isotope layer and a coating layer.

The drawing figures are not necessarily to scale.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is described in the context of a vascular liner such as a tubular graft for intraluminally bridging an aneurysm, defect or injury, or a stent for supporting and maintaining a vessel lumen following an angioplasty or other procedure for opening the lumen. It will be understood that the invention may be incorporated into prostheses of all types for maintaining patency or for contacting the walls of lumens of blood vessels or other body ducts, hollow organs or vessels and that the expression "body lumen" includes all such lumens.

Turning to FIG. 1, it depicts a prosthesis **10** constructed in accordance with an embodiment of the invention in relation to an exemplary stent placement system **100** that may be used to intraluminally introduce and release the stent **10** at a desired body site. Alternate deployment systems and useful deployment methods are disclosed in U.S. Pat. Nos. 5,405,379, 5,306,294 and 5,336,473, the disclosures of which are incorporated herein by reference.

The stent **10** is shown in its retracted state and partially deployed from the distal end **102** of a tubular introducer catheter **104**. The illustrated introducer catheter **104** has an inside diameter substantially equal to the outer diameter of the stent **10** when in its collapsed roll state. The catheter **104** is provided with at least one elongate lumen extending axially therethrough, for removably receiving a central core or pusher **106**. In the illustrated embodiment, pusher **106** comprises an elongate flexible tubular element having an outside diameter which is less than the inside diameter of the catheter **104**. The pusher **106** is therefore preferably provided with a stop **108** on the distal end thereof for permitting the pusher **106** to efficiently push at least one prosthesis **10** distally from the catheter **104**. In use, the pusher **106** will generally be held in an axially fixed position and the catheter proximally withdrawn to deploy the prosthesis **10**, as will be discussed below. Preferably, the catheter **104** is adapted to be introduced over a guidewire **110**, which is axially slidably received through the coiled prosthesis **10** and through the lumen within pusher element **106**.

As shown in FIG. 1, the prosthesis or stent **10** is formed of a sheet **11** that is rolled up into a tubular body **13** of a single layer or multiple overlapping layers of sheet **11**. The tubular body **13** therefore has a side wall formed of the rolled up sheet **11**, an inner lumen around the guide wire **110**, and an axial length extending, in the longitudinal direction of the introducer catheter **104** between proximal and distal tubular body ends. The proximal tubular body end butts against the stop **108**, and the distal tubular body end will generally be positioned near the distal end **102** of catheter **104**. The guide wire **110** guides introduction of the distal end **102** of the outer introducer catheter **104** including the stent **10** within it to a body lumen site for deployment of the stent **10** in a manner generally taught in the above-referenced '294 and '473 patents, incorporated herein by reference in their entireties.

The reduced implantation diameter of the tubular body **13** is dictated by the inside diameter of the catheter **104**. In an alternative embodiment of the placement system **100** such as that disclosed in the '294 patent, the outer sheath **104** is not used and cords (not shown in FIG. **1**) are used to restrain the sheet **11** in the collapsed roll state until the cords are withdrawn all in a manner taught in the above-incorporated '294 patents.

In accordance with a method of installation using the depicted placement system **100**, the perforated sheet **11** is rolled up into a tubular stent **13** such as by rolling the sheet **11** around a mandril (not illustrated). The rolled tubular body **13** is then loaded into the distal end **102** of the introduction catheter **104**, either at a point of manufacture, or at the clinical site. The radially outwardly directed bias of the tubular body **13**, as discussed in greater detail infra, causes the tubular body **13** to press radially outwardly against the interior wall of the catheter **104**, thereby retaining the tubular body **13** in position within the catheter **104**. The introducer catheter **104** and the stent **10** are thereafter introduced over the guide wire **110** and advanced transluminally to the desired body lumen site with the tubular body **13** restrained in the collapsed roll state. At the site, the pusher **106** is advanced distally with respect to the catheter **104** to expel the stent **10** out of the distal end opening of catheter **104**. Preferably, the catheter **104** is withdrawn proximally while the pusher **106** is maintained stationary in the vessel. The released tubular body **13** self expands in diameter to its expanded roll state constrained in size by the diameter of the body lumen at the site.

The placement system **100** of FIG. **1** and the method of placement described above provide one example of a system and method for collapsing the stent **10** and for effecting its introduction and release at the site that may be employed with the improved stent **10** of the present invention. Any of a variety of alternate deployment systems can also be used as will be apparent to persons of skill in the art in view of the disclosure herein.

Moreover, the perforation pattern of the stent sheet of the present invention may be incorporated into stents that are not self expanding and are expanded at the site by expansion mechanisms. In such a case, the stent expanded roll state would still have multiple layers of the sheet in the side wall thereof as shown in the remaining figures.

Returning to FIGS. **1–3**, the tubular body **13** is formed of a sheet **11** of biocompatible material rolled into a plurality of layers to form the side wall and a central lumen. The tubular body **13** therefore presents a plurality of adjacent arcuate layers of the sheet **11** rolled up in a direction transverse to the longitudinal direction and the longitudinal axis of the stent **10**. The sheet **11** possesses an inherent resilience and spring force that seeks to unwind the wound layers and expand the stent lumen as described in the above-incorporated '294 patent, for example. In the fully expanded roll state within a vessel, there are at least about 1½ to 4 or more fully overlapping layers that bear against one another under the spring force, when the prosthesis is intended to resist collapse. In an embodiment intended to deliver radiation but not also function as a mechanical support, a single complete circumference with no or minimal overlap may be sufficient.

In general, the optimum number of overlapping layers or fractional layers in the implanted, expanded configuration will depend upon a variety of factors as is discussed else-

where herein. For example, sufficient overlapping surface area to resist collapse under radially inwardly directed pressure from the artery is desirable. Factors such as sheet thickness, spring force, and effects of various coatings upon the coefficient of static friction may affect the minimum area of overlap necessary to resist collapse. Although excessive overlapping layers (e.g. 3 or 4 or 5 or more) provide increased radial strength, they may prohibit the use of a balloon to post dilate or size the stent following initial deployment. For applications in which post deployment dilatation is desired, a relatively fewer layers are preferred. Thus, overlap on the order of ½ layer or one full layer or 1½ layer or 2 layers or even 2½ layers may be desirable for stents intended for post deployment dilation. Additional considerations which affect the optimum overlap are disclosed elsewhere herein. In general, for any intended implanted diameter, sheet thickness, and surface material, the optimum number of overlaps for a target artery size can be readily determined through routine experimentation by those of skill in the art in view of the disclosure herein.

Turning to FIG. **2**, the sheet **11** is shown flattened out to illustrate the perforation pattern employed in a preferred embodiment of the present invention to assure that openings extend through the multiple layers of the rolled up sheet **11** forming the tubular body **13** in the expanded roll state. The sheet **11** has a sheet length SL providing the plurality of overlapping layers when the sheet **11** is rolled up in the length direction and a sheet width SW corresponding to the axial length of tubular body **13**. The sheet width SW and length SL in one 3 cm embodiment are on the order of about 30.0 mm and 116.0 mm, respectively, resulting in a tubular body length of about 30 mm. The sheet **11** may be formed of a biocompatible metal alloy, e.g., Elgiloy, in a foil of a thickness of about 0.0015 inches (about 0.038 mm).

It is contemplated that a sheet 11 having an SL of 116 mm and thickness of about 0.0015 inches may be wound into a collapsed roll state to fit within an introducer sheath lumen of about 3.9 mm in inside diameter and have an inner diameter of about 1.3 mm, in which the number of layers in the tubular member side wall approaches **18**. When released in situ, the outer diameter of the tubular member **13** may expand to between 12 mm and 18 mm, resulting in between 3 and 2 layers, respectively, forming the side wall of tubular member **13**.

In general, the length of the tubular body **13** (which will normally equal the sheet width of the sheet **11**) is selected to optimize performance of the prosthesis in the intended use environment. For example, in an application where the prosthesis is intended to be used as a graft for treating a tubular abdominal aortic aneurysm, the sheet width will generally be within the range of from about 75 mm to about 200 mm. Preferably, the sheet width is selected to provide a graft having an axial length which is greater than the length of the aneurysm or other diseased site being treated. Preferably, each of the proximal and distal ends of the graft will overlap with healthy vessel for a distance of at least about 10 mm. A relatively greater overlap, such as on the order of 15 mm or greater, may be desirable in straight sections of the aorta, to optimize anchoring and tacking down of the ends of the graft by way of neointimal growth.

The illustrated sheet **11** is provided with a plurality of perforation zones **30, 32, 34** and **30', 32'** and **34'**, arranged in first, second and third positions in first and second mirror image halves **40** and **40'**, respectively, spaced apart along sheet length SL as shown in FIG. **2**. In effect, the perforation zones **30, 32**, and **34** are arranged in respective first, second and third portions of the strip in a first row in the first half **40**, and the perforation zones **30', 32'** and **34'** are arranged in respective first, second and third portions of the strip in a second row in the second half **40'**. A plurality of elongated perforations **28** (shown in FIG. 6) are formed in each of the generally rectangular perforation zones **30, 32, 34, 30', 32'** and **34'**. Thus, each line in the parallel interior groups of lines in FIG. **2** represents a row of end-to-end perforations such as those illustrated in an enlarged fashion in FIG. **6**.

The first perforation zones **30, 30'** are each formed with a first plurality of elongated perforations **28** extending in parallel with one another in a first direction **50** parallel to the longitudinal axis of the sheet **11** and nominally designated as 0°. The second perforation zones **32** and **32'** are each formed with a second plurality of elongated perforations **28** extending in second and third directions **52** and **54**, respectively, at +45°, and –45°, respectively, to the longitudinal axis (the 0° direction **50**). The third perforation zones **34** and **34'** are formed with a third plurality of elongated perforations **28** extending at 90° to one another in the directions **54** and **52** respectively. In this manner, the perforations **28** in the adjacent perforation zones **32, 32'** and **34, 34'** are at an angle of 90° to one another and equalize bias forces that arise from the perforation directions **52** and **54** that would tend to cause the sheet **11** to twist when rolled up in the collapsed roll state or as the prosthesis expands to the expanded roll state. Other angles besides 90° may also be used, as long as the longitudinal axes of the elongated perforations are generally symmetric (opposing) across the longitudinal axis to cancel roll bias.

In the illustrated embodiment, each of the three rectangular perforation zones **30, 32, 34** and **30', 32' 34'** of the first and second halves **40, 40'** are of equal size. The widths of each perforation zones are somewhat smaller than one half the sheet width SW allowing for border and center bands of sheet material. The lengths of each perforation zone along the sheet length SL are substantially the same and are chosen in this case to substantially correspond to the chosen or target circumference of the resulting tubular body in the expanded roll state having substantially three overlapping layers.

The perforation zones **30, 32, 34** and **30', 32' 34'** of the first and second halves **40, 40'** are formed inside an edge border band **44** extending all the way around the edge of sheet **11** having a width of about 1.2 or 1.3 mm. Similarly, the adjacent perforation zones in each half **40** and **40'** are separated from one another by side border bands **45** having a width of about 1.2 mm–1.3 mm. A center border line area **46** of about the same width extends lengthwise down the center of sheet **11** and divides the sheet **11** into the longitudinally extending first and second halves **40** and **40'**.

In this manner, the border bands between the perforation zones are preferably minimized, and the first and second pairs of first, second and third zones occupy substantially the entire sheet **11**. However, the border bands do prevent the elongated perforations of each zone from encroaching one another or reaching the edges of the sheet **11** to preserve sheet **11** integrity.

Turning to FIG. **6**, one perforation pattern of a segment of the plurality of elongated perforations **28** of each zone is shown in enlarged detail. Each elongate perforation **28** is preferably about 1–3 mm in perforation length PL and between 0.10 mm and 0.50 mm in perforation width PW. The end to end and side to side separations **36** and **38** between adjacent perforations **28** is preferably about 0.2–0.5 mm in both cases. The perforations **28** are in parallel with directions **50, 52** and **54** in each of the perforation zones depicted in FIG. **2**.

Turning to FIGS. **4** and **5**, the stent **10** of the illustrated embodiment is depicted in one of the possible expanded roll state wherein the sheet **11** is rolled up in the sheet length direction SL in three overlapping rolled up sheet layers which together form the side wall **58** of tubular body **13**. Consequently, the perforation zones **30, 32,** and **34** in the first half **40** and **30', 32', 34'** in the second half **40'** overlap one another around most if not all of the perimeter of side wall **58**. A portion of the perforations **28** in the overlapping zones **30', 32'** and **34'** are also depicted in FIGS. **4** and **5** to illustrate the formation and maintenance of openings, e.g., as opening **60**, extending through the side wall **58**. The alignment of the perforations **28** in each overlapping zone **30', 32', 34'** and **30, 32, 34** provides a multiplicity of such spaced apart openings extending completely through the side wall. Given the dimensions and spacing of the perforations **28** stated above, each opening **60** is no greater in size than the perforation width PW. The spacings in the sheet length SL and sheet width SW directions between openings **60** is dependent on the number of layers formed when the sheet **11** is unrolled into the expanded roll state to fit into the vessel lumens.

The spaced apart openings **60** are formed due to the complementary interaction of the first direction **50** with the second and third directions **52** and **54** of the elongated perforations **28** in each overlapping zone. As is evident from FIGS. **4** and **5**, the alignment of the zones in the sheet length direction SL and the sheet width direction SW is not critical to the formation of the openings **60**. A lateral shift or twist in the rolled up tubular body **13** is tolerable as it still allows the openings **60** to form due to the interaction of the perforations **28** extending at the +45° and −45° directions **52** and **54** in the inner layers with the 0° direction **50** in the outermost layer. The likelihood of twisting is lessened by orienting the perforations **28** in each zone in the mirror image manner depicted in FIG. **2** but may occur to a slight extent.

Although FIGS. **4** and **5** show the tubular body **13** formed of three overlapping layers, it will be understood that the tubular body diameter may be increased or decreased, thereby decreasing or increasing, respectively, the number of overlapping layers, to accommodate a larger or smaller vessel lumen diameter. When the diameter is increased and the tubular body **13** is formed with two overlapping layers (at least in part), the openings **60** may need to be spaced closer together and be somewhat smaller than the openings **60** depicted in FIGS. **4** and **5**. When the diameter is decreased to a point where more than three overlapping layers are formed at least in part, the openings **60** may also be spaced further apart and be somewhat larger in size.

In this regard, the preferred embodiment of the stent described above and depicted in the drawings is preferably dimensioned to be used in vessels having a diameter in which the tubular body **13** is accommodated having one and one half, one and three quarters, two, three, four or five or more and any fraction therebetween of overlapping layers in its expanded roll state. A selection of stents **10** may be provided with the sheet length SL and the lengths of the perforation zones **30, 32, 34** and **30', 32', 34'** tailored to accommodate a particular range of body vessel lumen diameters. A selection of such stents may also be provided having different sheet widths SW to bridge vascular defects of differing lengths in the body vessel. The physician may select the appropriately dimensioned prosthesis **10** for the particular body vessel.

Preferably the second and third directions **52** and **54** are at +45° and −45°, respectively to the 0° direction **50**, and therefore extend to 90° to one another. These angles may also be varied as long as the perforations **28** extending at each angle overlie one another when the sheet **11** is rolled into the tubular body **13** and provide a suitable number of aligned openings **60** through the multiple layers of the side wall.

In the illustrated preferred embodiment, the perforation zones are arranged such that in the first half **40**, the first, second and third zones **30, 32, 34** are arranged across the center line border band **46** from the second, first and third zones **30', 32', 34'** of the second half **40'**, so that the second and third directions **52, 54** of the second and third zones **32, 32'** and **34, 34'** are adjacent to one another across the center border band **46** in order to balance twist biases induced in the sheet **11** by the second and third directions **52** and **54** of the elongated perforations **28**. The particular order in which these zones appear from the outer-most to the inner-most layers forming the size wall of tubular body **13** may be changed from the order depicted in FIGS. **2–5**. In any such configuration, the sheet **11** may be rolled up such that the first perforation zones **30, 30'** are in the inner-most layer rather than the outer-most layer as shown.

Moreover, while the preferred number of perforation zones in each half is three to provide a substantially three layer, tubular body in the expanded roll state, only two or more than three such perforation zones may be provided in each half to provide substantially two or more layers in the tubular body. The case of four perforation zones in each half to provide substantially four layers in the tubular side wall in the expanded roll state, an additional pair of side-by-side perforation zones may be provided both having elongated perforations extending at 90° to the length direction **50** of the sheet.

In addition, the above-described preferred embodiment of the stent of the present invention is provided with perforation zones formed in portions of first and second halves of the sheet on either side of the center line area **46** to thereby form parallel rows of perforation zones along the sheet length SL. It is also contemplated that additional rows of parallel perforation zones may be formed across the sheet width SW and extending the sheet length SL. A selection of directions **50, 52, 54** (or other suitable directions) for each perforation zone is to be made to offset the above described curl bias forces induced by the perforation directions so that the tendency of the sheet to twist out of alignment with the sheet length direction or 0° direction **50** when in the expanded roll state is minimized.

Although the sheet is preferably formed of metal foil, the invention may be practiced using sheets formed of biocompatible plastic materials or other suitable sheet materials.

The prostheses of the present invention may be employed as a graft bridging an aneurysm in a blood vessel and may be employed in the system depicted in the above-referenced '906 application. The prostheses of the present invention may be used in any of a variety of alternative applications where radial support is desired or channeling of blood is desired. Repair of a tear in the intimal wall of an artery or a repair of a dissecting aneurysm is contemplated. The present invention may also be utilized as a stent, such as following radial expansion of a stenosis by balloon angioplasty, laser ablation, rotational atherectomy, or other lesion modifying technique.

Although the above described stent **10** is preferably self-expanding, it will be understood that the perforation zones and complementary pattern may also be used in multi-layer sheet stents that are expanded by an expansion

mechanism such as a balloon catheter from the collapsed roll state to an expanded roll state in order to provide the openings **60** through the side wall of the tubular body formed on expansion.

The perforation pattern of the present invention allows the resulting openings **60** to be relatively numerous and small enough to avoid significant blood loss therethrough. Although the present invention has been described in terms of certain particular aperture shapes and patterns, any of a wide variety of aperture size, shape and distribution patterns can be utilized for any of the embodiments disclosed herein, and still accomplish the functional advantages of the present invention. In general, the aperture size and pattern should seek to produce a net aperture through the side wall of the prosthesis which is small enough to prevent substantial blood loss therethrough, and large enough to facilitate endothelial cell growth.

By "net aperture" opening, it is meant the effective cross section of the aperture which has a clear or tortuous passageway through each of the two or three or four or five or more adjacent layers of the sheet when rolled up into the expanded, implanted diameter. Thus, for example, referring to FIG. **5**, each slot in each of the three adjacent layers may have a width of about 0.2 mm and a length of about 3 mm. Due to the misalignment of the longitudinal axis of the overlaying apertures, the net opening **60** through the side wall **58** will be on the order of about 0.2 mm in diameter.

In general, net aperture openings of less than about 0.5 mm, preferably less than about 0.25 mm and more preferably less than about 0.10 mm are contemplated. Net aperture openings of about 0.05 mm or smaller may be preferred in some applications. The net aperture opening and aperture density preferably produce a blood or blood serum flow rate through the side wall within the range of from about 50 to about 3000 cc/cm^2/minute @ 120 mm Hg pressure. More preferably, the leak rate is less than about 200 and preferably no more than about 100 cc/cm^2/minute @ 120 mm Hg pressure. Aperture cross sections for round or nearly round apertures in a microporous embodiment are generally less than about 0.05 inches, often less than about 0.01 inches and is low as about 0.001 inches or less depending upon desired stent performance.

Net aperture dimensions much greater than the recited ranges may also work, but may delay the time until the apertures are sealed off by natural mechanisms. This may be undesirable in an application intended for use as a vascular graft, in which excessive blood loss through the wall of the aperture may be undesirable. In addition, the net aperture distribution should be such that will permit a continuous or substantially continuous layer of endothelial cell growth along the wall of the prosthesis. At the present time, it is believed that the endothelial cell growth will travel no more than about 0.125 inches along a continuous metal surface.

As recited supra., the minimum aperture size should be sufficient to permit endothelial cell growth therethrough. This may be accomplished in apertures having a net cross section measured in microns, with exact limits which can be established through routine experimentation by those of skill in the art. Thus, one hole pattern and distribution pattern for a porous sheet could involve the use of a laser perforation or other technique for producing hundreds or thousands or more of apertures per square centimeter. Distribution may be regular or random, as long as there exists a statistical likelihood that a continuous or tortuous aperture **60** will extend through each of the adjacent wall layers in the expanded, implanted diameter, at a distance of no further apart than about ⅛ or 1/10 of an inch as has been discussed.

One advantage of the aperture configuration and patterns illustrated in FIG. **2**, and other pattern designs not specifically illustrated but contemplated herein, is that an appropriate net aperture size will be achieved in the rolled implanted expanded prosthesis, throughout any of a variety of implanted diameters. Since the same stent or graft will optimally be useful in any of a range of vessel diameters, the optimal aperture pattern and distribution will permit the stent to expand from the insertion diameter to any of a variety of implanted diameters which will always achieve a net aperture distribution and dimension in accordance with the foregoing. Thus, the prosthesis of the present invention is expandable from an insertion diameter to any of a variety of implanted diameters and still achieve the endothelial cell growth objectives of the present invention.

As will be appreciated by those of skill in the art in view of the disclosure herein, the embodiments which utilize zones of apertures having a primary longitudinal axis may be provided with any of a variety of orientations with respect to each other. One consequence of certain aperture patterns is the introduction of roll bias in the final product. By roll bias, it is meant the tendency of the stent upon unwinding from the insertion diameter to the implanted diameter to unwind in a manner that spirals out in an axial direction, thereby extending the axial length of the stent. In applications where a roll bias is undesirable, perforation patterns, such as left- and right-hand mirror image patterns, have been found to assist in minimizing roll bias.

For example, although the orientation of the longitudinal slots in the multi-zone embodiment of FIG. **2** are 0° from the longitudinal axis, −45° and +45°, all longitudinal slots may alternatively be provided with the same orientation throughout the sheet. Preferably, to minimize roll bias, at least one zone or a group of zones will have an orientation of $-\theta$ to create a first roll bias, and an equivalent zone or groups of zones will have an orientation of $+\theta$, with respect to the longitudinal axis of the sheet to create an opposite roll bias. θ may range from about 10° to about 80°, preferably from about 30° to about 60°, and more preferably from about 40° to about 50° with respect to the longitudinal axis of the sheet. Alternatively, one or more groups of apertures may comprise oval or round holes, rectangular openings, or other geometric configurations, provided that the net aperture size and distribution in the wall of the finished stent when in the intended expanded diameter satisfies the functional requirements described above.

The apertures may be provided in any of a variety of manners which will be understood to those of skill in the art. For example, a sheet of material, such as Elgiloy, or any of a variety of stainless steel or other biocompatible materials having a sufficient spring force is provided. The sheet may then be laser etched, photo etched, perforated using electronic discharge technology or other means, depending upon the sheet thickness, physical properties of the alloy or polymer sheet and desired aperture diameters and patterns. In one embodiment of the invention, the apertures are produced using conventional photo etching technology. The etched sheet is then rolled up and restrained within about a 2½ cm restraining tube, and heated to approximately 900° F. for approximately 4 hours, to relieve stress. In general, the larger the diameter of the restraining tube during the heat stress relief step, the greater the spring force in the finished prosthesis. The heat treated prosthesis may then be tightly rolled and installed within a deployment catheter, or packaged for other use at the clinical site. Prior to loading or packaging, coatings may be added to the tubular prosthesis. Anticoagulants, such as heparin, endothelial cell growth

initiators, macrophage inflammation inhibitors or any of a variety of other drugs or coatings, may be utilized, as will be apparent to those of skill in the art in view of the disclosure herein.

Another feature of the prevent invention is the provision of an extremely low leading edge profile in the implanted prosthesis. The leading edge profile, or radial thickness of a prosthesis wall, as seen in a direction of blood flow, is believed to cause undesirable turbulence in the bloodstream. One conventional coronary artery stent, for example, has a leading edge profile on the order of 0.0055 inches. The spiral rolled construction of the present invention permits the use of very thin sheet material, which provides a relatively high radial strength for resistance to radial compression, as a function of total wall thickness. This allows blood flow turbulence to be minimized.

For example, in a stent having a sheet thickness of about 0.0015, rolled up to have three overlapping layers and a net wall thickness of about 0.0045 in accordance with the present invention, is expected to have a radial strength in excess of that for conventional nonrolled stents or grafts having a greater wall thickness. In general, radial deformation preferably begins within the range of from about 50 to about 760 mm Hg global radial pressure. Sheet thicknesses as low as 0.001 inches, and preferably as low as 0.0005 or less (to produce a leading edge profile of 0.0015 inches or less in a three layer as implanted prosthesis) are contemplated by the present inventor.

In accordance with an alternate embodiment of the present invention, the leading edge profile can be reduced by staggering the axial ends of the layers of the tubular stent. Thus, when the stent is rolled up into its normal expanded configuration within the vessel, each internal rolled layer is slightly inset from the previous layer thereby creating a stepped path for the blood interface rather than the full frontal face of several layers stacked on top of each other. This can be accomplished several different ways, as will be apparent to those of skill in the art in view of the disclosure herein. For example, tapering the unrolled sheet width such that it does not correspond to a regular rectangle can produce a stair step leading edge when in the rolled configuration. Alternatively, the sheet can be predisposed to roll into a slight telescoping configuration, thereby achieving a stepped leading edge profile.

Thus, for a three layer stent constructed from a sheet having a thickness of 0.001 inches, the leading edge profile can be reduced from 0.003 inches in a nonstepped configuration to three separate 0.001 inch steps. Each step can be axially spaced apart from the other step by any amount determined clinically desirable, such as within the range of from about 0.001 inches to about 0.01 inches or more. The axial run between adjacent steps can be optimized to produce the least turbulent leading edge profile, yet not adversely affect the structural integrity (eg radial strength) of the stent, as can be determined through routine experimentation by one of skill in the art in view of the particular application for the stent.

In addition, the tubular prosthesis of the present invention provides a relatively uniform leading edge. Many alternate stents and grafts have a jagged or angular leading edge, as a consequence of the wire construction or diamond patterns that may be cut into the wall of the prosthesis. The uniform leading edge is also believed to assist in minimizing leading edge turbulence. Blood flow turbulence may also be minimized, and compatibility of the prosthesis is optimized by the microporous apertures of the present invention, particularly when provided in a density and distribution as discussed above. The facilitation of a continuous endothelia cell coat along the interior wall of the stent is believed to make the stent appear to the blood and surrounding tissue more biocompatible than the material of the stent may otherwise appear to be.

Another advantage of the rolled foil design is that it spreads the radial force of the stent evenly over a large percentage of the vessel wall thereby reducing the localized stress on the medial layer and therefore it reduces or eliminates stress induced inflammation. It has been demonstrated in canine models (UCLA canine study #97097), under the direction of the present inventors, that a 16 mmx51 mm rolled foil stent of 0.002 inch thick nitinol, with a slot pattern similar to that described by this application, may be implanted in 6 mm canine femoral arteries for 30 days and cause virtually no inflammation. This is in contrast to balloon expandable stents that may cause severe inflammation of the vessel walls when implanted at high pressure in similar model.

Thus, in accordance with the present invention, the tubular prosthesis has sufficient contact area with the vessel wall to sufficiently distribute radial force from the implanted stent to the vessel wall to minimize the inflammatory response. Generally, the stent contacts in excess of about 50% of the area of the adjacent vessel wall. Preferably, the stent contacts in excess of about 65% or 80% or greater of the adjacent vessel wall. The surface contact area of microporous embodiments can be calculated based upon the aperture sizes disclosed elsewhere herein.

In accordance with another aspect of the present invention, there is provided a method and apparatus for treating a site in a body lumen by deploying a plurality of tubular supports or stents sequentially along the length of a treatment site. Thus, two or more stents can be positioned sequentially one after another directly against the vessel wall, or within a tubular graft as will be discussed in greater detail below.

Multiple sequential stenting in accordance with the present invention can provide a variety of advantages over conventional stenting techniques. For example, although many coronary artery lesions are relatively short (e.g., 1 cm), other vascular treatment sites may be as long as 5 or 10 cm or longer. Conventional balloon expandable stents are normally deployed using a single stent or single articulated stent per balloon catheter. Thus, where multiple stent treatment is desired, a number of separate balloon catheter entries must normally be used. Although longer stents may result in less total number of stents for a given axial treatment length, long stents may be difficult or impossible to navigate through tortuous and/or narrow vasculature. Even with a long stent, the fixed stent length limits clinical judgment. In addition, most or all practical stent designs or articulated stent segments tend to assume a generally linear configuration once deployed and expanded in a vessel. Thus, the expanded stent tends to straighten the vessel which may prevent stenting of lesions located in curved portions of the vessel. In addition, even in a relatively straight vessel, the linear nature of conventional expanded stents produces a risk of injury at the junction between the axial ends of the stent and the vessel wall.

Thus, in accordance with the present invention, a plurality of relatively short tubular stents are deployed one after another along a treatment length of a vessel. The axial length of each stent may be varied depending upon the desired clinical application. For example, in a coronary artery

application, multiple stents may each have an axial length of within the range of from about 0.25 cm to about 2 or 3 cm or longer. Although shorter stents may be used in some applications, stents having an aspect ratio of at least about one and often two or more may be desirable. The aspect ratio is the ratio of the length of the stent to the diameter in the expanded configuration, such that a 16 mm axial length stent positioned within an 8 mm diameter vessel exhibits an aspect ratio of two to one. Stents for use in the present aspect of the invention may be but are not necessarily provided with the various aperture patterns disclosed previously herein for, among other purposes, minimizing roll bias. Thus, relatively higher aspect ratios may be desired in tubular stents which have not been patterned to minimize roll bias.

In general, the number of stents delivered in a single procedure at a treatment site will be a function of the length of the treatment site, the length of the individual stents, and the spacing selected by the clinician between adjacent stents. In general, relatively shorter axial length per stent may be desirable if the treatment site is in a relatively curved portion of the vessel, as will be discussed.

Referring to FIG. **7**, there is illustrated a schematic cross-sectional view of a multiple stent deployment catheter **120** in accordance with the present aspect of the invention. The deployment catheter **120** comprises a proximal end **122**, a distal end **124** and an elongate flexible tubular body **126**. In general, a control **128** is provided on the proximal end **122** for manipulating the catheter **120** and controllably deploying one or more tubular stents **130**. The stents are illustrated as spaced apart for clarity, but would normally be in axial contact with each other within the delivery catheter.

In general, the elongate flexible tubular body **126** will have an outside diameter within the range of from about 1 mm to about 8 mm and at least one central lumen **132** having an inside diameter within the range from about 0.67 mm to about 7.5 mm. Any of a variety of conventional materials and techniques can be used for producing tubular body **126**, as are well known in the catheter construction arts. In general, for coronary artery applications, the tubular body **126** will have an axial length within the range of from about 135 cm to about 175 cm. For peripheral applications, the length of the tubular body will depend upon the distance between the percutaneous or surgical access site and the treatment site. For example, in a femoral-popliteal graft application, the length of tubular body **126** will generally be within the range of from about 50 cm to about 120 cm, and the outside diameter will range from about 1 mm to about 4 mm for a femoral-popliteal application and possibly larger for other applications.

One, and preferably two or more stents **130** are positioned within the distal end of lumen **132**. The stents **130** are preferably "self-expanding" such that they are maintained in a relatively small diameter configuration inside of lumen **132** but they expand radially outwardly when released from the catheter. Any of a variety of known self-expanding stents can be used, including spring coil, shape memory metal (e.g., Nitinol) as will be apparent to those of skill in the art. Preferably, however, a rolled flexible sheet type stent will be used.

In one embodiment of the invention, the catheter **120** is preloaded with the desired number of stents **130** either at the point of manufacture, or at the clinical site, prior to positioning within the patient. For example, two, three, four, five, six, seven, eight, nine, or as many as ten or more stents **130** can be positioned within the catheter **120** prior to insertion into the patient.

In one embodiment of the catheter **120**, the stents **130** are loaded in a proximal direction into the distal end of the lumen **132**. The total number of stents **130** for a given catheter design will depend upon the desired number of stents available for delivery (the clinician may choose not to use all stents loaded within the catheter **120**) as well as engineering reasons such as the coefficient of static friction between the stents **130** and the interior wall of lumen **132**. In embodiments intended to carry a relatively large number of stents **130**, a lubricous coating such as teflon or paralene or others known in the art may desirably be provided on the interior wall of the lumen **132** as well as on the outside surface of each stent **130**.

In an alternate embodiment, the lumen **132** has a substantially constant interior diameter throughout the entire axial length of the catheter **120**. In this embodiment, the stents **130** can be "breach" loaded into the proximal end of the catheter **120**. A pusher may then be utilized to advance the stents either one at a time or as a group distally through the lumen **132** into a deployment zone within the distal end of the catheter **120**. For breach loading designs of catheter **120**, additional stents **130** may be loaded into the catheter **120** while the catheter remains within the patient. For this purpose, the pusher is proximally withdrawn from the catheter, and additional stents as desired may be loaded into the proximal end of the catheter and advanced distally to the deployment zone. At that point, the catheter is positioned precisely by the clinician and the additional stent or stents may be deployed as desired.

For either the distally loaded stent or particularly the proximal loaded stent embodiments, it may be desirable to seek to minimize friction between the stent and the interior wall of lumen **132**. For example, lubricous coatings such as those identified before can be used.

In addition, it may be desirable to rotate the stent within lumen **32**, as the stent travels axially through the catheter. From the direction illustrated in FIG. *7a*, rotation of the stent **130** is preferably accomplished in a clockwise direction so that the radially outward most edge of the stent **130** trails against the interior wall of the lumen. In this manner, the stent tends to wind more tightly, and friction between the stent and catheter is reduced. Rotation can be accomplished by rotating the core **136**, and frictionally engaging the pusher **134** with the stent. Any of a variety of structures for imparting a rotation to the stent **130** can be readily envisioned by one of skill in the art in view of the disclosure herein.

The stents **130** are positioned distally of a deployment surface such as the distal surface of a pusher **134** for advancing the stents **130** distally out of the end of the catheter **120**. The pusher **134** is generally connected to or is the distal end of an elongate flexible axial force transmitting structure such as a central core or tubular body **136** which extends proximally throughout the length of the catheter.

Distal advancement of tubular body **136** with respect to the catheter **120** will deploy stents **130** from the distal end of the catheter **120** as will be apparent to those of skill in the art in view of the disclosure herein. In a preferred deployment method, the relative movement between the catheter **120** and core **136** is accomplished by holding the core **136** in an axially fixed position and retracting the catheter proximally until a stent **130** is deployed. Thus, the distal end of the catheter is positioned at the desired location for the distal end of the implanted stent prior to stent deployment.

Alternatively, the tubular body **136** may be replaced by a nontubular push wire, which runs in parallel to the guidewire

138. In an embodiment using a tubular support **136**, the guidewire **138** preferably runs axially through a central lumen in tube **136**, through pusher **134** and axially through the stents **130**.

Preferably, the proximal end of the catheter **122** is provided with a control **128** for controllably deploying the stents **130**. Preferably, the control **128** comprises a structure for indexed deployment of the stents **130**, such that one stent may be deployed at a time and under the direct control of the clinician. For example, control **128** may comprise a handle **140** and an actuator **142** such as a lever or trigger coupled to a ratchet structure **144**. The trigger **142** and ratchet **144** may be calibrated such that a single pull of the trigger **142** deploys a single stent **130**. In this manner, the clinician can deploy the stents **130** sequentially while proximally withdrawing the catheter **120** to produce a series of axially adjacent deployed stents.

Alternatively, the tubular body **136** can be provided with a plurality of visual indicia such as index lines, which are visible to the clinician on the proximal end of the catheter **120**. The clinician can manually advance the pusher **134** distally with respect to the proximal end **122** of the catheter **120** to deploy stents **130** as desired. Any of a wide variety of alternate deployment control structures can be readily designed, as will be apparent to those of skill in the art in view of the disclosure herein.

Referring to FIG. **8**, there is illustrated a plurality of stents **130** deployed serially in a curved portion of an artery **146**. The number of stents **130** used to treat a given axial length treatment site is largely within the judgment of the clinician, depending upon lesion morphology and other considerations. For example, a lesion or other treatment site having an axial length of about 12 cm to 14 cm may be treated using five 2 cm stents having a space between stents within the range of from about 0.1 cm to 1 cm. The spacing between adjacent stents can be varied considerably depending upon clinical judgment. In addition, the present invention permits the spacing of adjacent stents in a manner that prevents occlusion of branch arteries such as branch artery **148** illustrated in FIG. **8**.

Referring to FIG. **9**, there is disclosed one embodiment of a tubular graft and deployment catheter **160** such as might be used for a transluminal grafting procedure. The catheter **160** generally comprises an elongate flexible tubular body **162** having a proximal end **164** and a distal end **166**. Proximal end **164** is provided with a manifold **168** containing appropriate connectors as may be desired in view of the functionality of the catheter **160**. For example, an access port **169** is preferably axially aligned with the catheter **160** as is known in the art for receiving a guidewire **182**. Access port **169** is also provided with a stent deployment actuator **178**, which may be manipulated to deploy stent **172** from the distal end **166** of the catheter **160**. Deployment actuator **178** may comprise a plate **180** such as a radially outwardly extending annular flange attached to a push wire or tube **181**. In one embodiment, the distal surface on plate **180** is spaced proximally of the access port **169** by a sufficient distance that advancing plate **180** distally into contact with port **169** provides sufficient travel to deploy a single stent **172** from the distal end of the catheter. Preferably, actuator **178** is provided with a lumen (not illustrated) to accommodate guidewire **182**. Additional access ports such as dye port **171** may also be provided as desired.

In general, the distal end **166** of the catheter **160** is provided with a stent **172** and a flexible tubular graft **176**. Preferably, the stent **172** is connected to the graft **176**, either at a point beyond the distal end of the tubular body **162** or through one or more side openings on the tubular body **162**.

The distal end **166** in the illustrated embodiment is provided with an axially extending slot **170**. Slot **170** permits the rolled stent **172** to be positioned within the distal end of the tubular body **162** with a free end **174** of the rolled stent **172** extending through the slot **170**. In this manner, the stent **172** can be positioned fully within the catheter **162**, and be connected to a graft **176**. The graft **176** is connected at its distal end to the free end **174** such as through the use of any of a variety of adhesives, stitching, thermo-bonding, mechanical interfit, or the like. The vascular graft **176** trails proximally along the outside of tubular body **162**. Grafts **176** having lengths within the range of from about 2 cm to about 30 cm are contemplated, although other lengths may be desirable depending upon the clinical application. Any of a wide variety of known graft materials, such as dacron or polytetrafluoroethylene, may be utilized, togcether with any subsequently developed graft materials as will be apparent to those of skill in the art.

Referring to FIG. **11**, there is disclosed one embodiment of a distal end for a stent deployment catheter, which can be adapted for use on either the catheter design of FIG. **7** or FIG. **9** above. A generally cylindrical tip **200** is provided with a proximally extending annular flange **202**, adapted to fit within the tubular body **162**. Proximal flange **202** terminates at its proximal end in a stop surface **204**. Stop surface **204** is spaced axially apart from a complimentary stop surface **208** on the axially moveable actuator **206**. A guidewire lumen **207** is illustrated extending axially through the actuator **206**.

A stent compartment **210** is disposed distally of the actuator **206**. As will be apparent to those of skill in the art, the axial length of stent compartment **210** will be a function of the number of stents desirably loaded therein. Similarly, the axial space between stop surface **204** and complimentary stop surface **208** will correspond to the desired axial travel of the actuator **206** to fully deploy the stents contained in stent compartment **210**. Any of a wide variety of other specific structures can readily be devised for deploying self-expanding stents from the distal end of catheter **164**, **120** as will be apparent to those who have skill in the art in view of the disclosure herein.

In use, a surgical incision or percutaneous puncture is made to provide access to a vessel to be treated. The catheter **162** is thereafter inserted into the vessel and advanced transluminally until the stent **172** is positioned at or beyond the treatment zone from the perspective of the catheter **162**. The deployment structure is advanced distally with respect to the catheter **162**, so that the stent **172** is deployed from the distal end of the catheter **162**. Deployment of the stent **172** from the catheter **162** permits the stent **172** to assume its enlarged radial configuration within the vessel, thereby supporting the tubular graft **176** against the vessel wall. The catheter **162** may thereafter be proximally withdrawn, leaving the graft **176** extending from the stent **172** towards the clinician through the artery or other vessel.

The proximal end of the graft **176** may be secured such as through a surgical attachment procedure as is known in the art. Alternatively, the proximal end **176** may be secured within the vessel through the use of a second expandable stent deployed from the same catheter **162** or a separately introduced catheter. In a preferred embodiment, the catheter **162** contains at least the distal stent **172** and a proximal stent (not illustrated) for supporting the proximal end of the graft **176**. Thus, a procedure such as a femoral-popliteal bypass

can be accomplished percutaneously in accordance with the present invention without the need for a surgical cutdown and anastomosis.

In a further embodiment, as illustrated mid-procedure in FIG. **12**, the catheter **162** is provided with three or more stents, including the distal stent **172** and two or more additional self-expanding stents. In this manner, the catheter can be withdrawn proximally following placement of the distal stent **172**, and one or more stents can be positioned at intermediate locations between the proximal and distal ends of the graft **176**. A proximal most stent can be deployed at or about the proximal end of the graft **176**. In this manner, a plurality of supports can be positioned within a vascular graft, for providing intermediate support thereby enhancing patency of the graft along its entire length.

The multiple supported graft aspect of the present invention can be accomplished in a variety of ways, depending upon catheter design and clinical preference for a given procedure. For example, the distal stent **172** may be attached to the graft **176** as has been discussed. One or more intermediate supports **184** may also be attached to the graft **176**, such as by axially elongating the slot **170** in a proximal direction on catheter **160**, as will be apparent in view of the disclosure herein. This design ensures a predetermined spacing between axially adjacent intermediate supports **184** and distal end supports.

Alternatively, the axially spacing between adjacent supports is determined by the clinician during the procedure. In this application, the intermediate supports **184** are positioned within the catheter **160** in a manner described in connection with the catheter of FIG. **7**. Thus, axial distal displacement of a stent deployment surface **134** with respect to the catheter **160** controllably deploys the intermediate stents **184**.

Depending upon the length of the graft **176** and the spacing between adjacent supports, the clinician may or may not utilize all of the intermediate supports **184** in a given graft implantation. One of the supports **184** will preferably be positioned at or near the proximal end of the graft **176**, and will thus become the proximal attachment point of the graft.

In a relatively large vessel procedure, such as a femoral-popliteal bypass, the outside diameter of the catheter **160** is about 2–3 mm and the inside lumenal diameter of an expanded stent **184** will be on the order of about 4–10 mm. Thus, it may be possible for the physician to advance the catheter **160** distally through a previously implanted stent **184** to deploy additional intermediate stents **184** if the physician determines during the procedure that the spacing between adjacent stents **184** was undesirably large. Fluoroscopic or other visualization of the procedure in real time will permit the clinician to deploy a first number of supports **184**, evaluate the resulting patency of the lumen, and, if desired, deploy a second support or set of supports **184** as may appear warranted in view of the visualization of the patency of the graft lumen.

Proximal retraction of the catheter **160** following deployment of the distal stent **172** may cause a proximal motion of the graft **176** within the vessel. It may thus be desirable to anchor the distal stent **172** to the vessel wall or otherwise increase the coefficient of static friction between the stent **172** and the vessel wall. Although providing the stent **172** with a relatively larger radially outwardly directed expansion force may accomplish a sufficient anchoring of the stent **172** in the vessel, excess outward force may be medically undesirable.

As an alternative anchoring structure, the distal stent **172** and possibly also the intermediate and proximal stents **184** may be provided with a plurality of anchors. Referring to FIG. **13**, there is illustrated a flat sheet **186** from which the tubular stents **172** and **184** may be wrapped. The sheet **186** is provided with a plurality of slots or punch-outs **188** throughout at least a portion of the axial length of the sheet **186**. Due to the rolled configuration of the sheet (see FIG. **14**) in the as-used orientation, in which two or three or more overlapping layers of the sheet **186** will normally be present, anchors **188** need not be provided throughout the axial length of the sheet **186**.

When the stent is rolled as shown in FIG. **14**, the punch-outs **188** will tend to produce a radially outwardly inclined ramp **190** which can be used to anchor the graft **176** against the vessel wall.

A variety of objectives can be accomplished by coating or covering certain surfaces of any of the stents disclosed herein prior to implantation into the vessel. As used herein, the term "coating" is intended to cover generically any form of material which is adhered to or deposited on or adjacent the surface of the stent, such as a jacket or thin film, regardless of the composition, porosity, adhesion characteristics, thickness or biological activity or inactivity of the material.

For example, coatings can be used to affect the physical properties of the stent, such as the spring force or radial strength of the underlying material, or the cross-sectional area of the pores such as in the microporous embodiments disclosed previously. Other coatings can be selected for their biochemical reactivity or stability. For example, coatings which consist of or contain various prostaglandins, cAmp (cyclic AMP), aspirin, coumadin or heparin may be useful to inhibit platelet adhesion or reduce thrombogenicity. Other coatings may be selected to stimulate or inhibit neointimal growth, inhibit restenosis of other etiology, or accomplish other physical or biological activity-based results. Coatings as contemplated herein can be permanent, bioabsorbable, or otherwise transient in the intended use (aqueous/blood) environment.

Referring to FIG. **15**, there is disclosed an unrolled sheet **220** of the type which can be rolled into a tubular stent or prosthesis, as has been previously described. The sheet **220** can have a slotted aperture pattern, or randomly or regularly arranged round or irregular apertures as may be desired.

Although the sheet **220** will be described in terms of a stent which has approximately three overlapping layers in its implanted (in vivo) configuration, a three-layer structure is merely one example of the applicability of the present invention and is not intended to limit the scope of the invention to any particular number of overlapping layers. Instead, the description of the three-zoned embodiment of FIG. **15** serves to illustrate the three conceptual zones on a stent of the type disclosed herein, which has at least some overlap in the implanted configuration. The actual stent as expanded in vivo may have anywhere from about 1.2 revolutions or 1.5 revolutions to about 3 or 3.5 revolutions. In general, at least about 1.5 or about 2.0 revolutions (2 layers) will be desirable to produce sufficient radial strength, and in some applications, about 2.5 or 3 revolutions will be useful. The minimum number of in vivo layers desired for a given application may be affected by the lubricity of any coatings on the surface of the sheet **220**, as will be discussed.

Referring to FIG. **15**, the stent **220** can be conceptually divided into three zones. An inner zone **222** forms the inner wall of the stent when implanted. Thus, the inner facing

surface **228** of the inner zone **222** will be in contact with blood or other body fluid in the vessel.

An intermediate zone **224** will exist in any stent having more than 2.0 revolutions in the in vivo configuration. At least a portion of the interior surface **228** and of the exterior surface **230** of an intermediate zone **224** is shielded from direct contact with either blood flowing through the vessel or the vascular wall. Any contact between the intermediate zone **224** and blood or tissue in a full 3.0 revolution implanted stent will typically be limited to whatever biological or chemical contact may be made through the pores or apertures in the adjacent inner zone **222** or outer zone **226**.

Another example of a coating would be the use of this stent to deliver radioactive material to the site of a stenotic lesion. The sheet itself may comprise a radioisotope, or the sheet can be coated, clad, or implanted with a radioisotope. There are ample examples in the published literature of the preventative effects of irradiating smooth muscle to prevent the occurrence of restenosis. The problem has been the delivery of the radioactive particles to the site of the potential lesion. Radioactive rays such as gamma rays are so potent that they go through almost anything but thick lead and are therefore difficult to handle and deploy. Beta rays penetrate only very short distances and therefore must be almost in direct contact with the surface to be treated. BES devices that have been used to try to deliver radioactivity have not been successful because the radioactive struts of the BES device are sufficiently far apart from each other that they leave a blank spot in the area between struts. The microporous rolled foil stent on the other hand provides an ideal vehicle for delivering radioactive particles such as alpha or beta rays. For example, a sufficient length of the sheet to equal one circumference in the expanded state (e.g. the outer ⅓ or ½ of the 3 or 2 layer rolled foil stent) could contain the radioactive material. Upon deployment at a lesion the outer layer of the stent would reside against the arterial wall and deliver the radioactivity directly to the area in apposition to the stent. The inner layer or layers of the stent would act as a radiation barrier and protect the blood from unnecessary radiation contamination. The nature and density of the inner layers of the stent material may even reflect a portion of the radiation back to the vessel wall. In either case be it absorption or reflection of the radioactive rays, the protective inner layer of this multi layer stent design will allow higher and more uniform radiation doses to be delivered to the vessel wall than would otherwise be acceptable to an open structure BES type stent or single layer foil stent.

The preferred radioactive coatings are comprised of one or more layers of materials placed upon the stent which serves as the substrate **310**, as shown in FIGS. **20A–20D**. There may or may not be a clear visual or physical distinction between the various layers in the coating because each layer need not be a discrete structural element of the coating. As the layers including the layer formed by the stent itself bond together to form the coating, they may become blended, alloyed or intermingled to form what looks and acts like a single layer having a somewhat heterogeneous composition. For this reason, the various layers as defined and used herein are intended to denote the functional characteristics of the components or help denote what process steps are used in their formation, whether through the use of discrete structural layers or layers blended with neighboring layers, the selection of which will be apparent to those of skill in the art in view of the particular materials and components used.

The radioactive coatings all comprise an isotope layer **312**. The isotope layer **312**, comprises metal salt wherein a plurality of the ions in the salt are radioisotopes. The radioisotope can be almost any species available, such as alpha, beta or gamma emitting, as is discussed below. The isotope layer **312** may further comprise one or more metals from which the metal salt of the layer is derived. The isotope layer preferably has a density in the range of 10^{10}–10^{25} atoms/cm^2, more preferably about 10^{13}–10^{15} atoms/cm^2, most preferably about 10^{14} atoms/cm^2 and is has a thickness of preferably 10014 10,000 Angstroms thick, more preferably about 500–1500 Angstroms thick.

As used herein, the term "metal salt" refers to a compound comprised of at least one anion and at least one cation. The anions and cations of the metal salt may be either simple (monatomic) ions such as Al^{3+}, Cl^- and Ag^{1+}, or complex (polyatomic) ions such as PO_4^{3-} and WO_4^{2-}. At least one of the ions in the metal salt compound should comprise a metal. The term "metal" as used herein means all metals, including, for example, semimetals, alkali metals, and alkaline earth metals. Preferably metals are selected from the transition metals or main group of the Periodic Table of the Elements. The term "metal salt" as used herein in its broadest sense can encompass metal oxides.

Preferably, the isotope in the isotope layer is selected from the group of gamma emitters with energies less than about 300 keV including I-125, Pd-103, As-73, and Gd-153, or the high energy beta group (E_{max}>1.5 meV) including P-32, Y-90 and W/Re-188. Other isotopes not currently mentioned, can be utilized by the invention described herein. The selection of these isotopes, however, allows the source to be shielded in a material such as leaded acrylic in commercially available thickness of 15–30 mm, or in a lead tube of approximately 0.3–0.5 mm wall thickness. Some of the other isotopes which may be deemed suitable for use in the present invention or for a particular intended use, include Au-198, Ir-192, Co-60, Co-58, Ru-106, Rh-106, Cu-64, Ga-67, Fe-59, and Sr-90. The selection of an isotope may be influenced by its chemical and radiation properties.

The radioactive coatings of the present invention may further comprise at least one tie layer **311**. The tie layer **311** lies between the stent substrate **310** and isotope layer **312** and may act to increase the tenacity of attachment of the isotope layer **312** to the stent substrate **310**. The tie layer **311** may comprise adhesives, chemically activated surfaces, a chemical coating layer, an organic or inorganic compound, metal, metal oxide, metal salt, or metal alloy. Preferably the tie layer **311** is 100 to 10,000 Angstroms thick, more preferably 200 to 500 Angstroms.

The radioactive coatings of the present invention may further comprise one or more coating layers **314**. The coating layer **314**, may act as a sealing means to protect the isotope layer from mechanical abrasion or other injury which may strip the isotope layer of radioisotopes and thus reduce its activity. Furthermore, the coating layer may inhibit migration or other leaking of isotope in an aqueous (blood) environment. Addition of a coating layer may provide sufficient protection for the device to be classified as a sealed radiation source, i.e. one that has less than 5 nCi of removable activity. Each coating layer is preferably 1–30 μm thick, more preferably 10–20 μm thick.

The coating may be a metal or plastic. Plastic coating materials are preferably biocompatible, but not excessively biodegradable. Preferred materials include cyanoacrylates, acrylics, ethylene methyl acrylate, ethylene methyl acrylate/acrylic acid (EMA/AA), urethanes, thermal plastic urethane (TPU), PBVC, PVDC, and the like. Metal coatings can be used as well, with metals used preferably being bio-stable,

such as titanium. For example, platinum, gold, or titanium may be vapor deposited on a surface to encapsulate the isotope layer.

Referring to FIG. **20**A, a schematic of a cross-section of one embodiment of radioactive-coated stent is shown. An isotope layer **312** is disposed on the stent substrate **310**.

Referring to FIG. **20**B schematic of a cross-section of a second embodiment of radioactive-coated stent is shown. The bottom layer is the stent substrate **310**, the second or middle layer is the isotope layer **312**, and the outer layer is the coating layer **314**.

Referring to FIG. **20**C schematic of cross-section of a third embodiment of the radioactive-coated stent is shown. The bottom layer is the stent **310**, the second or middle layer is the tie layer **311**, and the outer layer is the isotope layer **312**.

Referring to FIG. **20**D, a schematic of a cross-sections of a fourth embodiment of the radioactive-coated stent of the present invention is shown. This embodiment comprises the stent substrate layer **310**, tie layer **311**, isotope layer **312**, and coating layer **314**.

Some of the difficulties associated with a lack of consistent dosing which is found with radiation delivery stents of the prior art, as discussed above, could be overcome through the use of longer half-life isotopes. Compared to the example above wherein three stents were implanted with P-32 to a level of 10 μCi using the Hehrlein method resulting in a dose variation of 29% at 7 days and 50% at 14 days, for stents implanted with an isotope with a 60-day half-life, the dose variation between maximum and minimum over the fourteen-day time frame would be reduced to 15%, and over a 7-day period to just 8%. The total dose for the longer half-life isotope will be greater, however the effective dose and dose rate remains to be determined. It is generally known that radiation dose can be increased if it is fractionated, or given over extended periods. Only experimentation can answer this question. However, if a long half-life isotope eventually proves effective, the lowest amount of radiation required to perform treatment is always preferable to any higher amount for safety reasons.

In general, the desired dose appears to be at least about 40 Gray within the first five half-lives of implantation, delivered to a depth of about 1 mm into the vessel wall, or about 20 Gray delivered to a depth of about 0.5 mm into the vessel wall, along the entire length of the source. That implies an activity of about 1 microCurie per centimeter length of stent. The dose may range as high as about 500 Gray at a depth of about 0.5 mm in five half-lives of implantation, along the length of the stent, or an activity of about 25 microCuries per centimeter of stent length. Ideal dosing for a particular clinical environment can be determined through routine experimentation by those of skill in the art, and may in certain applications fall outside of the foregoing ranges. Advantageously, the isotope attachment of the present invention permits the present invention to accommodate any of a wide range of desired dosing capabilities as will be appreciated by those of skill in the art in view of the disclosure herein.

Activity and lifetime of sources can be manipulated by the choice of isotope. The relatively rapid time of decay and concomitant loss of "strength" of short half-life isotopes may present product problems in addition to manufacturing problems. Because the isotope is contained on an implanted substrate and has a short half-life, a lack of consistent dosing may result. Take for example, P-32 implanted on three stents at the same time to a level of 10 μCi using the method described in the above-cited paper by Hehrlein (*Circulation*, 1996). Assume all stents are prepared and available for implantation on day 0. If the first stent is implanted immediately, the second after 7.1 days (one half of a half-life), and the third after 14.3 days (one half-life), then the total dose delivered by the second and third stents, as compared to the first stent, is 29% less for the second stent and 50% less for the third stent. It should be pointed out that the standard of practice for allowable variation in administered dose is 10%.

The radioisotopes used in the radiation delivery sources of the present invention may be beta or gamma emitters, or both, and may have any of a wide range of half-lives, both long and short. The particular isotope, as well as the concentration of the isotope in the source which determines the dose, can be chosen by one skilled in the art to serve the needs of a particular application. In a recent paper presented by Howard Amols at the January 1998 Scripps Clinic Conference on Intravascular Radiation Therapy entitled "Choosing the Right Isotope: What's New? Insights into Isotopes or Why Is it so Hard to Find the Ideal Isotope?," the author states that the best isotope choice from the perspective of both physics and dosimetry would be a photon source with an energy greater than 3 MeV and a half-life greater than 7 days. Shirish K. Jani, in a lecture entitled "Does the Perfect Isotope Exist?" at the same conference states that the perfect isotope for vascular brachytherapy would exhibit a low dose gradient, low dose levels to surrounding body tissues, manageable radiation exposure levels around the patient and a long half-life. Iodine-125 (I-125, half-life 60 days) and tungsten-188/rhenium-188 (W/Re-188, half-life 70 days) are candidates to meet these criteria, and also have long half-lives, and thus are two especially preferred radioisotopes for use in the present invention. Preferred radioisotopes used in the radiation delivery sources of the present invention may be purchased from Oak Ridge National Laboratory (Oak Ridge, Tenn.), New England Nuclear (NEN) or any other commercial suppliers of radioisotopes.

Preferred methods of making the isotope layer of the coating of the present invention may begin with either a stent substrate to be coated directly or a tie layer to which the isotope layer is to be bound. Preferred methods comprise exposing surfaces to fluids comprising reactants or isotopes. Such fluids may be gaseous (including plasma or vapor) or liquid (such as solutions), with liquid solutions being preferred. As such, the methods below are described in terms of liquid solutions.

Preferred methods of making the isotope layer of the radioactive coating of the present invention comprise, in part, either one or both of the following solution processes: (1) oxidation in an acidic solution to form a metal salt from a metal; and (2) ion exchange wherein ions at or near the surface of the metal salt are exchanged with those present in a solution. The first process is based on differences in oxidation-reduction potentials, and the second process is based on differences in solubility. These processes will be taken in turn.

In the first process, the equilibrium is driven by principles of oxidation-reduction (redox). A metal, in the form of a pure metal or part of an alloy, may be converted to a metal salt when it is placed in solution comprising an oxidizing agent. Many metals, including those in preferred embodiments discussed below, can be readily oxidized in solution to form metal cations, which may then form salts with anions in solution.

Whether or not a particular reaction of an oxidizing agent and a metal will occur spontaneously can be predicted by

reference to a standard table of half-cell potentials such as that in *CRC Handbook of Chemistry and Physics*, (CRC Press). If the sum of the potentials of the oxidation half-reaction and the reduction half-reaction is positive, then the reaction will occur spontaneously.

For example, it can be predicted that when silver is added to an acid solution of sodium chlorite, the silver will be oxidized. When added to the solution, sodium chlorite ($NaClO_2$) disproportionates to form hypochlorous acid and chlorine dioxide, which is capable of oxidizing silver as shown below:

$Ag \longrightarrow Ag^+ + e^-$ (ox)	Emf = -0.80 V
$ClO_2 + e^- \longrightarrow ClO_2$ (red)	Emf = 1.16 V
$Ag + ClO_2 + e^- \longrightarrow Ag^+ + ClO_2$	Emf = 0.36 V

In addition to the reaction shown above, the hypochlorous acid undergoes a redox reaction whereby chloride ions are produced which then couple with the silver cations to form silver chloride.

The second process is a solubility-driven ion exchange. When, for example, two anions are placed in solution with a given cation, there is a driving force which results in the formation of the metal salt which is less soluble/more insoluble. Because it is difficult to compare solubilities and thus predict behavior when the relative terms "soluble" and "insoluble" are used, solubility is related to a type of equilibrium constant, the solubility product or K_{sp} in order to quantify the degree of solubility for a given compound. The solubility product is equal to the concentrations of the dissociated ions of the salt at equilibrium, that is for salt AB, $K_{sp}=[A^+][B^-]$ wherein $[A^+]$ and $[B^-]$ are the concentrations of the A cation and the B anion, respectively. If a salt is fairly soluble, the concentrations of its component ions in solution will be relatively high, leading to a relatively large K_{sp}. On the other hand, if a salt is fairly insoluble, most of it will be in solid form, leading to low concentrations of the ions and a relatively small K_{sp}. Thus, when comparing two salts of the same metal, the salt with the lower K_{sp} is the more insoluble of the two. Solubility products for most common compounds can be found in reference texts such as the *CRC Handbook of Chemistry and Physics* (CRC Press).

The salts silver chloride (AgCl, $K_{sp}=1.77\times10^{-10}$) and silver iodide (AgI, $K_{sp}=8.51\times10^{-17}$) can be used to illustrate the principle of solubility driven ion exchange. The solubility products for these compounds are both fairly low, but K_{sp} for silver iodide is lower by nearly 7 powers of ten, indicating that it is more insoluble than silver chloride. Thus, if solid silver chloride is placed in a solution containing iodide ions, the equilibrium lies on the side of the silver iodide, and the chloride ions will exchange with the iodide ions so that the more insoluble silver iodide is formed. On the other hand, if silver iodide is placed into a solution containing chloride ions, the ion exchange will not take place. In this manner, chloride ions in silver chloride coated on the surface of a substrate can be replaced by ^{125}I anions to form a radiation source of the present invention.

The metal salt layer which is the starting point for the above solution ion exchange process may be formed by a redox process such as that described above, or it may be applied directly by means of sputtering, vapor deposition, or other techniques known in the art.

Alternatively, if a redox process described above is performed using an oxidizing solution containing a radioisotope, for example $H_3{}^{32}PO_4$, the radioisotope-containing metal salt layer may be obtained directly, eliminating the need for the ion exchange.

Another preferred method for making radioactive-coated stents of the present invention comprises oxidizing a metal, such as those bound to or incorporated in the stent substrate, and then binding an isotope to the metal oxide. The step in which the metal is oxidized preferably occurs spontaneously in air. Thus, metals such as aluminum and copper, which readily and spontaneously undergo oxidation to form their respective oxides, are preferred. Oxide formation occurs when the metal is exposed to air, but may be enhanced or increased by exposure to oxygen-enriched atmospheres or increased temperature. The binding of the isotope is preferably performed by immersing the metal oxide in a solution containing isotope ions, either simple or complex. The attraction between the metal oxide and the isotope ions is such that the isotope ions will bind to the metal oxide rather than existing free in solution. This binding or "plating" process may occur either with or without displacement of ions from the metal oxide.

There are several advantages to using the processes above to place active isotopes on a stent as opposed to the conventional techniques of ion implantation of radioisotopes and nuclear bombardment. One advantage is that unwanted isotopes are not formed. As discussed above with reference to Hehrlein '177, neutron activation of a stent produces numerous isotopes which makes it very difficult to control the dose provided by the stent.

An advantage of the present method is that it does not create large quantities of radioactive waste. By using the correct quantity of radioisotope solution, very little waste is produced. Isotopes which are not incorporated into a given source remain in solution and may be used on another source. Unlike radioactive ion implantation, there is no machine chamber filled with stray isotopes which must be cleaned and safely discarded.

Another advantage of the present invention is that the production process lends itself to batch processing. The attachment of metal layers, such as those which act as tie layers or to which isotopes are later bound, can be done in very large volumes using common chemical attachment techniques found in the semiconductor, solar energy, and packaging industries such as vapor deposition, electrodeposition, ion plating, ion implantation and sputtering. The radioisotopes are most commonly provided in solutions, so the isotope ion exchange or plating step is as simple as soaking the metal salt or metal oxide coated substrate in a solution of isotope. This step can be done in either very small or very large batch sizes, allowing the amount of radiation in the process to be limited accordingly.

Yet another advantage of the present method is that it allows use of isotopes which cannot be readily obtained on a solid source by the other means known in the art. With the proper choice of materials and solutions and the disclosure herein, one skilled in the art would be able to create a reaction scheme to make a salt containing the most of the desirable therapeutic radioisotopes. Furthermore, by using particular long-lived isotopes, a radiation source with a longer half-life can be produced which is capable of delivering a dose with less variation between maximum and minimum. Use of an isotope with a longer half-life may provide for a radiation source which is capable of lowering the amount of radioactivity necessary to perform its function over that which incorporates a short-lived isotope.

Another advantage of the present invention is that the radioisotopes are held by strong atomic-level bonding interactions, and which are highly resistant to leaching or release under physiological conditions. Additionally, the use of ionic bonding is especially useful for radioisotope species

such as iodine-125, as the salt form holds the normally volatile iodine atoms in place.

Another benefit to the solution processes described herein is that the density of activity of a given isotope or multiple isotopes may be controlled by simply controlling the time of immersion and/or the density and amount of metal salt or tie layer on the stent.

The basic method, as discussed in part above, comprises providing a stent and forming a coating comprising an insoluble metal salt with at least one radioactive isotope species thereon.

One preferred embodiment of radioactive-coated stent of the present invention is that which has an isotope layer comprising the gamma-emitting isotope ^{125}I. As mentioned previously, ^{125}I meets the criteria of an "ideal" isotope as defined by Amols and Jani. One method for making a coated stent having an isotope layer comprising ^{125}I is that which uses both solution methods discussed above. First, a stent is provided with silver in the metal alloy or elemental silver is attached to the surface of the stent using well-known methods such as ion implantation, vapor deposition, sputtering, electroplating, or rolling. The silver is then converted to silver chloride (AgCl) via an oxidation-reduction solution process such as that described above, which uses an acidic solution of sodium chlorite to reduce the silver and produce silver chloride. Then the silver chloride coated stent is immersed into an ion exchange solution of sodium iodide in the form of $Na^{125}I$, wherein the AgCl is converted to $Ag^{125}I$ on the surface of the stent. This manufacturing process may be performed quickly, easily and efficiently. In addition, the 1-125 with a half-life of 60 days would provide an equivalent or lower dose of radiotherapy for a longer period of time.

As an alternative to the above method, silver chloride could be directly deposited to the stent surface by means of vapor deposition or other method known in the art, and then immersed in the ion exchange solution containing $Na^{125}I$.

In an experiment done to demonstrate activity which may be achieved by the methods described herein, silver foil having a surface area of 4 cm^2 was immersed in a solution of 6M HCl and 1M $NaClO_2$ in a 10:1 ratio. A portion of the silver was converted to silver chloride. The foil was then immersed in a bath having about 2 ml of solution. The solution in the bath had about 0.07% $Na^{125}I$ in NaI, and was prepared by dissolving 0.5 mg NaI in 2 ml water and adding 4.6 mCi ^{125}I into solution. Following immersion, the resulting activity of the foil was measured at 2 mCi, which, when the amount of carrier (non-radioactive) iodine is factored in, corresponds to about 10^{18} atoms of iodine attached to the sheet. In a carrier free solution, this number of I-125 ions would result in an activity of 3 Ci per 4 cm^2 of substrate. This is 30,000 times the required activity for a 10 μCi stent.

Another preferred embodiment of radioactive-coated stent of the present invention is that which has an isotope layer comprising ^{32}P. A coating having an isotope layer comprising ^{32}P can be made by methods similar to that described above for ^{125}I using P-32 in the form of orthophosphoric acid ($H_3{}^{32}PO_4$) (New England Nuclear). First, a stent is provided. The stent may be manufactured to contain zinc or a zinc alloy, or it may be coated with zinc or a zinc alloy by vapor deposition or other methods known in the art. The zinc may then be converted to a relatively insoluble salt such as zinc fluoride (ZnF_2, $K_{sp}=3.04\times10^{-2}$) via an oxidation-reduction process similar to that discussed above. The stent is then activated by immersing the zinc fluoride coated stent in a solution containing phosphate ion in the form of $^{32}PO_4{}^{3-}$ or a soluble phosphate salt, whereby the more soluble fluoride ion is exchanged for phosphate to form zinc phosphate ($Zn_3(PO_4)_2$, $K_{sp}=5\times10^{-36}$).

Alternatively, the stent may be directly coated with zinc fluoride or other similarly insoluble salt by vapor deposition or other means known in the art, and then placed in an ion exchange solution. Yet another alternative is to use an oxidizing solution containing $H_3{}^{32}PO_4$ so that the zinc is directly converted to zinc phosphate containing the radioisotope, thus eliminating the ion-exchange step.

There is an additional advantage to using $Zn_3(^{32}PO_4)_2$ in the isotope layer. Zinc phosphate is a stable molecule and is often used in the automotive industry for paint adhesion to galvanized steel. Zinc phosphate has anticorrosive characteristics of its own, and has been used in the past to increase the corrosion resistance of steel. A zinc phosphate coating on a steel stent may be an advantage to the stent even in the case that it is not coated by a radioactive layer.

Yet another preferred embodiment of radioactive coating of the present invention is that which has an isotope layer comprising tungsten-188 (W-188 or ^{188}W) Tungsten-188 undergoes beta decay to become rhenium-188 (Re-188 or ^{188}Re). Rhenium-188 undergoes beta decay as well, but emits a much higher energy particle than in W-188 decay. The W-188 has a much longer half-life than does Re-188, thus the W-188 almost continuously creates more Re-188. This process is known as "generator," and the generator isotopes are referred to together by the shorthand W/Re-188 to indicate the relationship between the species. Generators are attractive for use in radiation delivery devices because they combine the energy levels of a short half-life species with the durability of the long half-life species. It is a general rule that particle energy and half-life are inversely proportional, and that long half-life species are more economical and practical to work with than short half-life species.

W/Re-188 is a beta emitting isotope with an energy about 10% higher than P-32. Where I-125 was discussed as a perfect gamma emitting isotope, W/Re-188 fits the criteria of both Amols and Jani for a perfect beta emitting species for IVRT. The advantage of the W/Re-188 stent would be that the dose would be consistently administered over a long period of time. The half-life of W-188 is 70 days as compared to 14 days for the P-32. This represents a consistent dose rate as Re-188, itself a beta emitting isotope, is being produced by the decay of tungsten for a longer period of time.

Tungsten, in the form of tungstate ion ($WO_4{}^{2-}$) may be readily attached to an oxidized aluminum surface to produce a W/Re-188-containing radiation delivery source of the present invention. An aluminum oxide surface may be attached to the stent by sputtering Al_2O_3, or Al can be attached by implantation or deposition, followed by an oxidation step. Ambient environment will facilitate the formation of Al_2O_3 from aluminum which can be accelerated by increasing the temperature and/or using an oxygen-rich atmosphere. The aluminum oxide surface may then be immersed in a tungstate containing solution, such as an acidic solution of sodium tungstate ($Na_2{}^{188}WO_4$), in order to attach the W-188 to the alumina surface.

Tungsten may also be applied together with a phosphate in a manner similar to that disclosed by Larsen in U.S. Pat. No. 5,550,006, which is hereby incorporated into the present disclosure by this reference thereto. The method disclosed in Larsen is claimed for use in increasing adhesion of organic resists for printed circuits. The method was used to perform a phosphate conversion coating onto copper. This method may find its application in the radiation delivery device of

the present invention in that many polymers and metals other than copper may be coated with this solution. In this method, phosphate may be in the form of $^{32}PO_4^{3-}$, tungstate may be in the form of $^{188}WO_4^{2-}$, or any combination of the isotopes in radioactive or stable form may be used.

Combinations of various isotopes provide another preferred embodiment in that, for example, beta-emitting isotopes may be combined with gamma-emitting isotopes where gamma isotopes can deliver dosage to greater depths.

Radioactive coatings comprising other isotopes can be made by procedures similar or analogous to the preferred embodiments disclosed above, using materials appropriate for the chemistry of the isotope to be included.

In some embodiments of the radiation delivery source of the present invention, it may be desirable to provide a tie layer, onto which the isotope layer can be placed. The tie layer may comprise adhesives, chemically activated surfaces, a chemical coating layer, or an organic or inorganic compound. Preferably the tie layer is a layer of metal, metal oxide, metal salt or alloy. Depositing a metal-type layer may allow an alloying process to take place, which will enhance the tenacity of attachment of the metal salt, and hence the isotope species. This is common in the semiconductor industry, wherein a chromium layer is used as an initial layer in the deposition of gold. The chromium is alloyed with the gold in order to increase the strength at which the gold is bound to the substrate. If, for example, the isotope layer comprises a zinc salt, a metal such as copper or aluminum may be used as the tie layer. The tie layer may also be in the form of an oxide that provides oxygen to chemically bind the atoms of the metal salt layer thereby increasing the tenacity of attachment.

The first metal layer to which the isotope layer is attached may comprise any suitable metal or metal oxide. The layer may be deposited by vapor deposition, sputtering, ion plating, ion implantation, electrodeposition, or other method. When the tie layer is present, there may or may not be a clear distinction between the tie layer and the isotope layer. In performing its function, and depending on the chemistry of the materials involved, the tie layer may become blended, alloyed or intermingled with the isotope layer, thus blurring the lines between the layers. For many of the same reasons, the distinction between the tie layer and a metal-containing substrate layer may also be blurred. In these cases, the term tie layer is meant to be a functional or process-defining definition; rather than a reference to a physically distinct layer of the radiation delivery source.

Although the stents of the present invention may have isotopes which are sufficiently adherent without further treatment, in some embodiments of the present invention, it may be desirable to place an outer coating layer on the stent. An outer coating can provide further advantages for the radioactive-coated stent of the present invention in that the coating can help provide additional means to bind the layers of the source together. Perhaps more importantly, an outer coating can increase the abrasion resistance of the radioactive-coated stent.

Sealed radioactive sources are those which have less than 5 nCi of removable activity. By providing a coating on the stent which covers at least the isotope layer, the source can be protected from unwanted loss of activity due to mechanical abrasion of the surface of the source. This is very important, both for providing safe devices for the patient which leave radioisotopes behind only where they are desired, and for monitoring dosage to ensure that the dose which is to be provided by a stent source will actually reach the treatment site, and not be significantly diminished due to loss of isotope from abrasion which may occur during handling, including implantation. It also helps insure that, once the stent is positioned, the radioisotopes will remain at the placement site and not be washed downstream.

Coating materials are preferably biocompatible, but not excessively biodegradable. Preferred materials include cyanoacrylates (Loctite, Hartford, Conn.), acrylics, ethylene methyl acrylate (Exxon Chemical Co., Houston, Tex.), ethylene methyl acrylate/acrylic acid (EMA/AA) (Exxon Chemical Co., Houston, Tex.), urethanes and thermal plastic urethane (TPU) (BF Goodrich, Richfield, Ohio), PVDC (Saran, Dow Chemical, Midland, Mich.), PBVC, and the like. Other preferred coatings may comprise other biocompatible materials, drugs or similar compounds, such as heparin. Many methods are available to perform the coating process, such as dip or immersion coating, spray coating, spin coating, or gravure. The curing technique may be any of the various techniques available, such as air, heat, or UV. Preferably the thickness of the coating which is formed is 1 μm to 30 μm more preferably 10 μm to 20 μm.

One preferred embodiment of the present invention has a coating that is formed with cyanoacrylate. Another preferred coating layer is that formed by ethylene methyl acrylate/acrylic acid (EMA/AA). An aqueous dispersion of this coating material, preferably having a viscosity less than **100** centipoise, allows for use of any of the above-mentioned coating methods. UV curable polyurethane acrylate is also useful as a coating layer material. Yet another preferred coating layer is that formed by SARAN. Such a layer may be formed, for example, by immersing the source or a portion thereof into a melt of SARAN or a solution containing SARAN.

The coating layer may also be formed by a spin coating process. Spin coating the thin film source finds advantage in the flexibility to use coating materials having a wide range of viscosities. Low viscosity liquids may be spun on slowly, while a higher viscosity liquid may be spun at a higher velocity to maintain a thin coating. The substrate may be held in place by fixturing or by vacuum during the spin coating process. In an experiment, a dispersion of cyanoacrylate in acetone was dispensed on top of the metal salt surface while the substrate was rotated at 8000 rpm for five minutes. The resulting thickness of the coating was about 6.5 μm (0.00025 inch). When this specimen, having the spin-coated surface curable coating of cyanoacrylate was extracted in saline for 8 hours at 50° C., the amount of radioactivity extracted was negligible.

An outer zone **226** surrounds the outer surface of the implanted tubular stent, such that an exterior facing surface **230** of the outer zone **226** will be in contact with the vessel wall.

As will be understood by those of skill in the art, in a stent **220** intended for placement in a vessel dimensioned such that the stent will have two complete overlapping layers in the implanted configuration, the central zone **224** will disappear, and the interior facing surface **228** of the inner zone **222** will be in direct contact with the blood, and the exterior facing surface **230** of outer zone **226** will be in contact with the vessel wall.

The unique construction of the rolled multi-layer tubular stent of the present invention permits the inclusion of a coating on the entire sheet **220**, or selected portions of the sheet **220**, to accomplish any of a variety of objectives. For example, at least the interior facing surface **228** of the inner zone **222**, and possibly also the exterior facing surface **230** of inner zone **222**, is coated in one embodiment with a biocompatible material to reduce thrombogenicity. Any of a

variety of materials, such as Parylene (Specialty Coating Systems, Inc., Indianapolis, Ind., 46241); heparin (such as a photolink heparin coating from BSI Corporation, Eden Prairie, Minn. 55344); PTFE spray, or others as will be understood by those of ordinary skill in the art, can be used. Due to the eventual neointimal growth on the interior surface of the stent, the antithrombogenic coating can be temporary (e.g., roughly on the order of about one to two weeks).

At least the exterior facing surface **230** of the outer zone **226**, and possibly also the interior facing surface **228** of outer zone **226**, and the entire intermediate zone **224**, may be left exposed metal. The contact between the metal exterior surface **230** and the vessel wall may desirably stimulate neointimal growth through the stent.

Thus, the tubular stent formed from sheet **220** can conveniently have a metal outer surface **230** for contacting the vessel wall and stimulating neointimal growth, and a biocompatible coating on the interior facing surface **228** for minimizing the thrombogenicity of the stent.

The rolled configuration of the present invention permits any combination of coated and uncoated surfaces on the finished stent. Thus, the blood contacting surface can be provided with a first coating, and the tissue contacting surface can be provided with a second coating which is different than the first coating. Alternatively, either the blood contacting surface or the tissue contacting surface can be left uncoated while the other surface is provided with a coating. In a stent having an intermediate zone **224**, the intermediate zone can be provided on one or both surfaces with a coating, such as to inhibit cellular proliferation, to moderate chemical communication, or other purposes as desired.

The coatings may be applied in accordance with any of a variety of techniques, as will be apparent to those of skill in the art in view of the disclosure herein. For example, the sheet **220** may be dipped into a reservoir of coating or coating precursor material, in an embodiment where at least a portion of both the interior facing surface **228** and exterior facing surface **230** is to be coated. For example, the sheet **220** can be dipped into the coating material to a depth of from about ¼ of the length of the sheet to about ½ the length of the sheet, and preferably in the area of about ⅓ the length of the sheet, such as to coat the inner zone **222** or the outer zone **226**. The other end of the sheet can thereafter be dipped into a second coating material, so that the rolled tubular support will have a dissimilar material on the interior surface than the exterior facing surface.

Alternatively, the coating material can be applied such as by spraying the sheet or portions of the sheet, using techniques known in the art. Spraying permits selective coating of one side of the sheet, such as either interior facing surface **228** or exterior facing surface **230** or portions thereof. Through the use of fixturing tools or masking techniques, a portion of one side of the sheet **220** can be coated using spraying techniques. The remainder of the sheet can be left uncoated metal, or can be provided with a dissimilar coating.

In an embodiment where, for example, a bare metal surface desirably is placed in contact with the vessel wall, and a coated surface is desirably placed in contact with the bloodstream, it may be convenient to spray coat the entire interior facing surface **228**, even though only a portion, such as inner zone **222**, will be in contact with the bloodstream. However, coating on the sheet **220** where it will be eclipsed by an intermediate zone **224**, for example, will add unnecessary thickness to the sheet. In general, it is desirable to maintain sheet thickness as low as possible, thereby minimizing the introduction cross-sectional area of the tubular stent. Thus, some estimation of the expanded configuration of the stent (e.g., approximately 0.5 layers overlap, 1 layer overlap, 1.5 layers overlap, 2 layers overlap, 2.5 layers overlap, 3 layers overlap, or other), should be made and taken into account during the coating process so that only a sufficient surface area of the sheet **220** is coated to provide a coating over the relevant surface on the finished stent.

The above-identified coatings may have thicknesses on the order of several molecular layers. In an alternate embodiment, the coating may take the form of a relatively thicker cover such as a film or jacket, such as having a thickness measured in ten thousandths or one thousandths of an inch or greater.

In the thick coating embodiments, the coating can be used to accomplish a variety of physical property objectives, such as controlling the pore size of the microporous apertures through the stent wall. Sheets **220** can be produced using EDM technology having apertures as low as on the order of about 0.001 inches (approximately 25 microns). Smaller apertures can be provided by covering a sheet having relatively large apertures with a coating to produce a reduced aperture size.

Thin films having controlled aperture size for use with this aspect of the present invention have relatively little structural integrity (e.g. PTFE film having a porosity of about 25 to 250 ml of water/Cm2/min @ 120 mm HG pressure, and a thickness on the order of 25 to 50 microns and cannot therefore be conveniently used by themselves in a stent application. However, when applied to the sheet **220** of the present invention the sheet **200** provides sufficient support to produce a functional tubular stent, while the supported film controls the aperture size of the stent. In addition, the film can operate to reduce thrombogenicity or other biological functions. Thin films, such as expanded PTFE film having a thickness lower than about 10 microns and preferably lower than about 5 microns, can be used for this purpose. Generally, aperture sizes in the film are within the range from about 2 to 10 microns.

In accordance with another embodiment of the present invention, the thin film or other coating can be used as an isolation layer to moderate biological communication between the outside and the inside of the tubular prosthesis. For example, a central zone, such as intermediate zone **224** of a microporous sheet **220**, may be coated on one or both sides in the flat state with a thin layer (e.g., from about 0.0004 to about 0.006 inches) of PTFE, ePTFE, or other suitable biocompatible isolation material. The covering may be applied in either a complete or partial manner to the inside only, the outside only, or to both sides of the sheet to create the isolation barrier. The isolation barrier separates the flow of blood from the wall of the vessel. In one embodiment, the isolation barrier covering is supplied to the middle 30% to 40% of the length of the sheet **220**.

In the deployed in vivo state, the covered stent will isolate the blood flow from the wall of an artery and/or a lesion, aneurysm, perforation, or other defect, with the wall of the artery. In the partially covered isolation layer embodiment, an uncoated microporous foil stent layer is exposed to the arterial wall on the outside of the stent and to the blood flow on the inside of the stent. These uncoated microporous layers allow for neointimal tissue growth and adherence to the microporous surface of the stent, while the isolation barrier reduces or eliminates the stimulation of smooth muscle cell proliferation caused by triggering components within the blood.

In accordance with another aspect of the present invention, the flexible sheet is configured to permit perfu-

sion through branch vessels, such as the renal vessels in an abdominal aortic aneurysm application. Referring to FIG. **16**, there is disclosed a sheet **240** configured to permit branch vessel perfusion. The sheet **240** comprises at least one microporous zone **242** and at least one perfusion zone **244**. The microporous zone **242** and perfusion zone **244** are oriented on the sheet **240** such that when the sheet **240** is rolled into a tubular prosthesis, the prosthesis will have a perfusion zone **244** and a microporous zone **242** thereon. In one embodiment, the perfusion zone **244** is disposed adjacent one end of the stent. In another embodiment, the perfusion zone **244** is positioned in between the two axial ends of the stent, and spaced apart from the axial ends of the stent. The precise axial location of the perfusion zone **244** along the length of an implanted stent can be varied, depending upon the intended implanted location of the tubular prosthesis relative to the branch artery.

In general, the microporous zone **242** may have aperture size and/or orientation patterns in accordance with any of the previously disclosed embodiments. The perfusion zone **244** is preferably provided with a plurality of apertures **246** which will generally be significantly larger in diameter than the micropores in microporous zone **242**. In this manner, the net aperture size through the side wall of the rolled stent will be sufficient to permit perfusion through the side wall of the stent and down the branch artery. In the illustrated embodiment, the perfusion zone **244** is provided with two or three or more oval apertures having a long axis diameter that is 1.5 to 3 times the diameter of the branching vessel, and a short axis diameter that is 1.25 to 2 times the branching vessel. Alternatively, the apertures **246** can be rectangular, separated by a plurality of transverse struts. Specific aperture cross-sectional areas and patterns can be varied, according to the desired degree of branch artery perfusion, as will be apparent to those of skill in the art in view of the disclosure herein.

In accordance with another aspect of the present invention, there is provided a modification to the rolled sheet to ensure that the ends of the sheet conform to the wall of the cylinder when the stent is implanted in a vessel. See, e.g., FIGS. **17–19**. One characteristic of the design of a rolled foil sheet **250**, is that the inner and outer terminal ends **252, 254** will separate from the circumference defined by the rest of the rolled sheet unless a modification is made to the spring force (sometimes referred to herein by reference to flexibility) at the terminal ends. The terminal end are defined for this purpose as the area within approximately the last ¼ to ½ inch of either end of the sheet for a foil that is, for example, 0.002 inches in thickness and made from a material such as nitinol or Elgiloy and about 26 to 76 mm long.

Inside the rolled foil, this separation of the terminal end **252** manifests itself as a short segment of stent wall that forms a chord across a section of the circumference of the central lumen of the stent. This chord section may be as much as about ¼ inch in length when the stent is rolled to a diameter of about 8 mm. This chord section creates a small axial channel separate from the central lumen created by placing the stent in a tubular structure such as a blood vessel.

At the outer end **254** of the stent, the terminal end of the foil forms a tangential flap which does not conform to the circumference of the tube when the stent is rolled to a diameter of about 8 mm or less. The flap becomes longer and more acute as the stent is rolled tighter and it becomes shorter and less arcuate as the stent diameter becomes larger. At about 16 mm in diameter the flap almost disappears as the end of the foil conforms to the circumference of the tubular stent. This effect creates a small separation layer when the stent is placed inside a rigid tube or it results in a point of concentrated stress if the stent is placed inside a flexible tubular vessel such as a blood vessel.

The two separation layers described above are a function of the thickness of the sheet material, the modulus of elasticity (Young's modulus) of the material and the radius of the arc around which the foil is to be bent. With two materials of equal modulus of elasticity but different thickness are bent around a similar radius, the thicker material will tend to create a greater diversion from the fixed radius of the tube. If the material thickness is held constant and the modulus of elasticity is varied, the material with the greater modulus of elasticity will form the greater departure from the circumference of the tube and so forth. In this example, the departures from the radius are caused by the action of the spring force within the material used to create the stent. In this example, the material is 0.002 inch thick nitinol. When the stent is rolled up to form a tube, the flat sheet is first flexed into an arc. The lengths of stent on either side of the middle of the arc act as lever arms and the resistance in the middle of the arc acts as a fulcrum. As the arc is progressively formed into a tube the ends will meet. As one end overlaps the other end, a spiral tube is formed. As the diameter of the tube decreases and the ends are continuously wrapped around the tube to create multiple layers, the lever arms are continuously shortened. As long as the lever arms are sufficiently long to overcome the spring force of the material created by the arc, or the arc is sufficiently large that the spring force is negligible, then the material will take the shape of the established arc and a spiral tube will be formed with multiple apposed layers. When the lever arms become too short to overcome the spring force of the material, or the radius becomes sufficiently short that the spring force increases beyond what the lever arms can overcome, then the ends will depart from the radius defined by the tube and create the chord section and flap at the terminal ends as described above.

Any of several structures which proportionately reduce the spring force near the ends **252, 254** of the foil as the lever arms are shortened, will allow the terminal zones or ends to more closely approximate the curvature of the defined tube. In the embodiment of FIGS. **17** and **18**, the sheet **250** has a cross-sectional metal content of approximately 67% at a reference point **256** just prior to the defined terminal ends **252, 254**. The sheet **250** has terminal ends **252, 254** that contain elliptical holes which become progressively larger as each row of holes approaches the corresponding end of the sheet. The first row **258** of elliptical holes represents about a 65% metal content; the last row **260** of elliptical holes represents about a 38% metal content.

Referring to the embodiment illustrated in FIG. **18**, each of the apertures in the terminal zone or end **252** (or **254**) is a generally elliptical hole having a length which is about twice the dimension of the width. The aperture centers in each row are spaced approximately 2.00 mm apart along a plane which is transverse to the longitudinal axis of the sheet. The apertures in the least flexible row **258** have a width of about 0.4 mm, and the apertures in the most flexible row **260** have a width of about 0.9 mm. The apertures in row **262** have a width of about 0.5 mm, row **264** have a width of about 0.6 mm, **266** have a width of about 0.7 mm, and **268** have a width of about 0.8 mm. The length of the zone **252** is about 5.3 mm on a sheet **250** having an overall length of about 51 mm, and a width of about 6.0 mm. That particular embodiment comprises a nitinol sheet having a thickness of about 0.002 inches (0.051 mm).

As more and more metal is removed from the terminal ends, the spring force is diminished proportionately. For this

example, the progressive reduction in spring force at the ends allows the stent to form a more perfect cylinder when rolled into a diameter of 6 to 8 mm. These terminal end sections may be longer for thicker metal, higher modulus of elasticity, or for a tighter radius in proportion to the changes is lever arm length. Conversely, more metal may be removed at a higher rate to achieve even more compliance with the desired radius.

FIG. **19** illustrates an alternate embodiment of the design. The terminal end **254** on sheet **250** is provided with a plurality of axially extending supports **270** which are spaced apart to provide a plurality of apertures **272**. The support **270** in the illustrated embodiment tapers from a relatively larger width at a first end **274** to a relatively smaller width at a second end **276** proximate the end of the sheet. In this manner, the aperture **272** is provided with a complementary trapezoidal shape, to provide a gradual increase in lateral flexibility in the sheet in the direction of the terminal end of the sheet **250**. In one embodiment, the apertures **272** are provided in a nitinol sheet having a thickness of about 0.0020 inches, an axial length of about 51 mm and a width of about 6.0 mm. The length of the terminal end **254** is approximately 5.3 mm. The sheet is provided with 4 supports **270** apart from the edges of the sheet. Each support has a width of about 1.24 mm at the first end **274** and about 0.7 mm at the second end **276**.

In another design, holes of a given diameter are spaced more closely together near the edge of the sheet thus allowing more holes per row and removing more metal per row to reduce spring force. Other designs may include holes of any shape, cone-shaped slots, serrated ends, tapered ends, changes in metal thickness through etching, drawing, rolling or other means known to those skilled in the art which would result in spring force reduction at the critical terminal ends, as defined above.

Thus, the benefits of the present invention can be accomplished through any of a variety of structures which provide a gradual increase in flexibility towards the axial ends of the sheet. In general, the sheet may be considered to be divided into a central zone, having a first terminal end on a first end thereof and a second terminal end on a second end thereof. In many embodiments, the central zone will have a relatively constant flexibility or spring force characteristics throughout its axial length. Each of the terminal ends will have a relatively increasing degree of flexibility throughout their axial lengths, to permit the axial ends of the sheet to conform to a portion of either the inside or outside surface of the cylindrical configuration assumed by the sheet when implanted in a vessel.

Although the present invention has been described in terms of certain preferred embodiments, variations of the invention will become apparent to those of skill in the art in view of the disclosure herein. Accordingly, the scope of the invention is intended to be limited solely by the attached claims, and not by specific structural recitations contained herein.

What is claimed is:

1. A radioactive tubular prosthesis, comprising:

a flexible sheet having a first edge and a second edge, the sheet rollable into a tube such that the first edge is disposed on the inside of the tube and the second edge is disposed on the outside of the tube;

a first transition zone near the first edge; and

a second transition zone near the second edge;

wherein the first transition zone has an increasing flexibility in the direction of the first edge, and the second transition zone has an increasing flexibility in the direction of the second edge, wherein the increased flexibility is achieved by having increasingly less sheet material in the first and second transition zones in the direction of the first and second edges respectively, and at least a portion of the sheet has a radioactive coating.

2. A tubular prosthesis as in claim **1**, wherein the sheet further comprises an intermediate zone of relatively constant flexibility between the first and second transition zones.

3. A tubular prosthesis as in claim **2**, wherein the first transition zone has an axial length of no more than about 20% of the axial length of the sheet.

4. A tubular prosthesis as in claim **1**, wherein the first transition zone comprises a series of apertures, said apertures becoming prooressively larger in the direction of the first edge.

5. A tubular prosthesis as in claim **1**, wherein the first transition zone comprises a series of apertures, said apertures becoming more numerous in the direction of the first edge.

6. A tubular prosthesis as in claim **1**, wherein the first transition zone comprises a series of trapezoidal apertures ninning axially along the length of the first transition zone, said trapezoidal apertures having their shorter parallel side pointing away from the first edge.

7. A tubular prosthesis as in claim **2**, wherein the first transition zone is thinnest at the first edge, becoming progressively thicker in the direction of the intermediate zone.

8. A tubular prosthesis as in claim **5**, wherein the apertures are sized within the range of from about 2 to 10 microns.

9. A self expandable radioactive tubular prosthesis having a plurality of ports through the side wall thereof, the prosthesis comprising a flexible sheet having a plurality of perforations therein rolled a first number of revolutions about an axis into a first, insertion diameter, the prosthesis radially expandable under its own bias by unrolling to a substantially cylindrical prosthesis having second, implanted diameter having a second, smaller number of revolutions, wherein some of the perforations are inclined at an anile with respect to the axis which is different from the inclination of other of the perforations with respect to the axis, and a sufficient number of perforations through adjacent layers of the sheet align to produce a plurality of ports extending all the way through the side wall of the prosthesis, the sheet provided with zones of differing spring strength so that an inner most revolution of the sheet conforms substantially to the cylinder, and at least a portion of the sheet has a coating comprising at least one radioisotope.

10. A tubular prosthesis, comprising:

a flexible sheet, having a longitudinal axis and at least first, second, and third groups of apertures extending therethrough;

the first group comprising a first plurality of parallel slots inclined at a first angle with respect to the longitudinal axis;

the second group comprising a second plurality of parallel slots inclined at a second angle with respect to the longitudinal axis;

the first, second, and third groups of apertures arranged on the sheet such that when the sheet is wrapped about an axis through at least about three revolutions to form a tubular prosthesis, apertures from the first, second, and third groups align to produce a plurality of ports extending through the side wall of the prosthesis; and

a radioactive coating on at least a portion of the sheet comprising at least one radioisotope.

11. A radioactive intraluminal stent implantable in a body vessel lumen, comprising:

a tubular body having a side wall and an inner lumen with an axial length extending between first and second ends of the tubular body, said tubular body formed of a sheet of bio-compatible material forming said side wall and inner lumen when placed in the vessel lumen in an expanded roll state, said sheet having a sheet length providing said first and second overlapping layers when said sheet is in the expanded roll state and a sheet width corresponding to said axial length; and

first and second perforation zones formed in first and second portions of said sheet displaced from one another along said sheet length, said first perforation zone having a first plurality of elongated perforations extending in parallel with one another in a first direction, and said second perforation zone having a second plurality of elongated perforations extending in parallel with one another in a second direction differing from said first direction; and

at least one transition zone on the sheet having a different spring force than at least one other portion of the sheet, transition zone exposed to the inner lumen; and

a radioactive coating on at least a portion of said sheet, wherein the first and second perforation zones substantially overlap one another when said sheet is rolled up into said tubular body having at least two layers in the vessel lumen and provide openings in said side wall through aligned portions of said elongated perforations.

* * * * *

US005762631A

United States Patent [19]

Klein

[11] Patent Number: 5,762,631

[45] Date of Patent: Jun. 9, 1998

[54] **METHOD AND SYSTEM FOR REDUCED FRICTION INTRODUCTION OF COAXIAL CATHETERS**

[75] Inventor: **Enrique J. Klein**, Los Altos, Calif.

[73] Assignee: **Localmed, Inc.**, Palo Alto, Calif.

[21] Appl. No.: **502,693**

[22] Filed: **Jul. 14, 1995**

[51] **Int. Cl.**[6] **A61M 5/00**; B29C 63/00

[52] **U.S. Cl.** **604/171**; 604/264; 604/280; 264/171.12; 264/172.1

[58] **Field of Search** 604/264, 280, 604/282, 171, 96, 101, 104; 264/171.12, 172.1, 173, 209.4, 284, 150; 606/192, 194, 108

[56] **References Cited**

U.S. PATENT DOCUMENTS

1,596,754	8/1926	Moschelle .	
3,872,893	3/1975	Roberts	264/172.1
4,410,476	10/1983	Redding et al.	264/172.1
4,421,810	12/1983	Rasmussen	264/172.1
4,681,570	7/1987	Dalton	604/282
4,689,174	8/1987	Lupke	264/172.1
4,900,314	2/1990	Quackenbush	604/282
5,054,501	10/1991	Chuttani et al.	128/772
5,122,125	6/1992	Deuss	604/282
5,147,317	9/1992	Shank et al.	604/164
5,217,440	6/1993	Frassica	604/282
5,244,619	9/1993	Burnham	264/173
5,337,733	8/1994	Bauerfeind et al.	604/282
5,404,887	4/1995	Prather	128/772
5,417,208	5/1995	Winkler	604/280
5,445,624	8/1995	Jimenez	604/280
5,496,292	3/1996	Burnham	604/282
5,571,086	11/1996	Kaplan et al.	604/96

FOREIGN PATENT DOCUMENTS

WO 92/19308	11/1992	WIPO .
WO 93/23105	11/1993	WIPO .

OTHER PUBLICATIONS

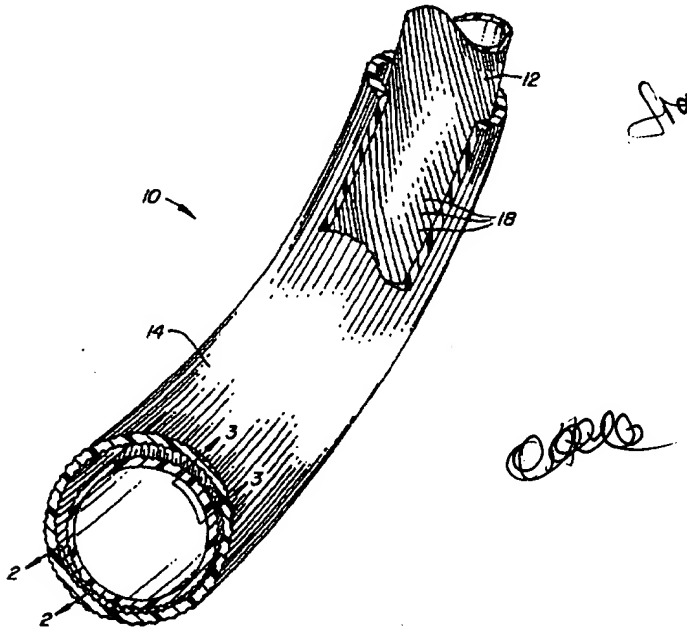
Product Brochure–Trio 14 "Re–engineering Over–the–Wire Balloon Technology," Scimed®. © 1994 Scimed Life Systems.

Primary Examiner—Robert A. Clarke
Assistant Examiner—David J. Cho
Attorney, Agent, or Firm—Townsend And Townsend And Crew LLP

[57] **ABSTRACT**

Catheter systems comprising a base catheter and a sleeve catheter are modified to have reduced sliding friction therebetween. The sleeve catheter is received over the base catheter, and an inner luminal surface of the sleeve catheter or outer surface of the base catheter is modified to have surface irregularities to reduce sliding friction. Preferably, the surface irregularities are circumferentially-spaced-apart V-spaced peaks. Such peaks may be formed by fabricating tubular catheter bodies in an extrusion tool having a mold or die with correspondingly shaped V-shaped grooves therein. Alternatively, the surface irregularities may be imparted using a mold or mandrel which is placed over or in a tubular catheter body, where the desired geometry is transferred by heating the catheter.

13 Claims, 4 Drawing Sheets



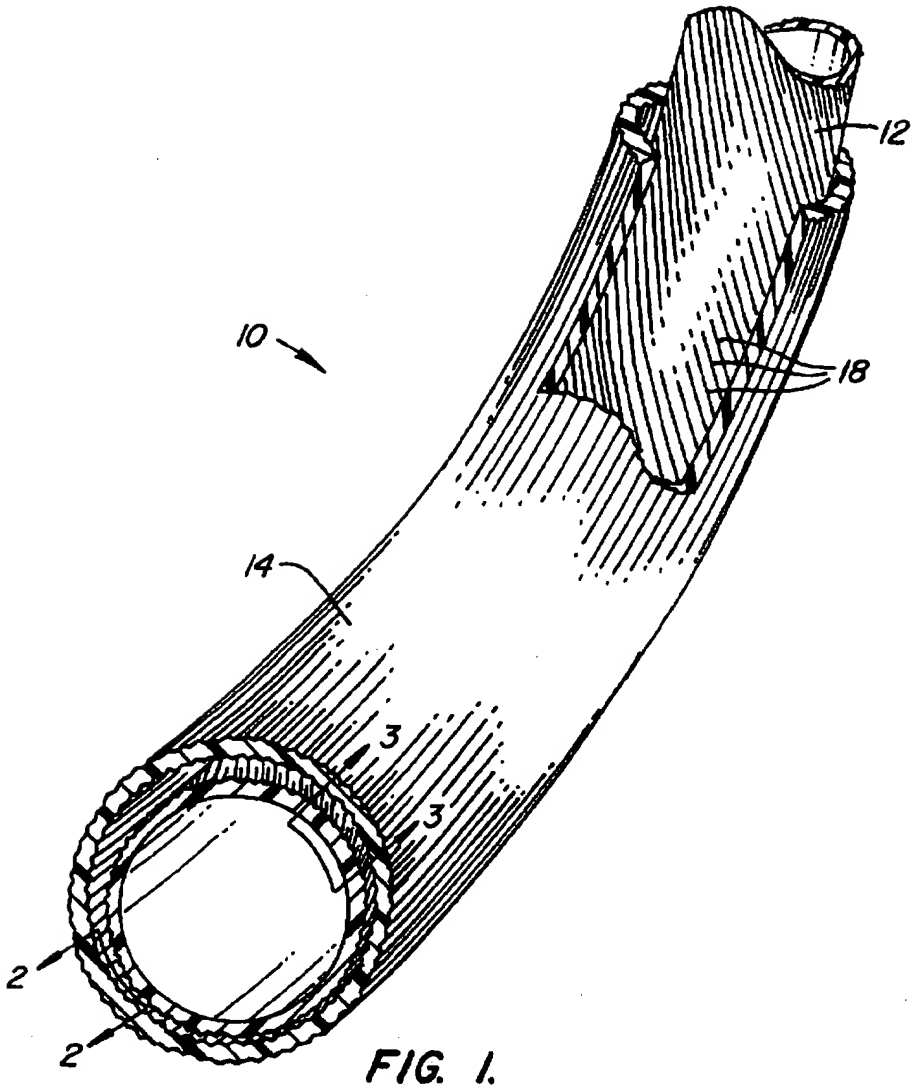


FIG. 1.

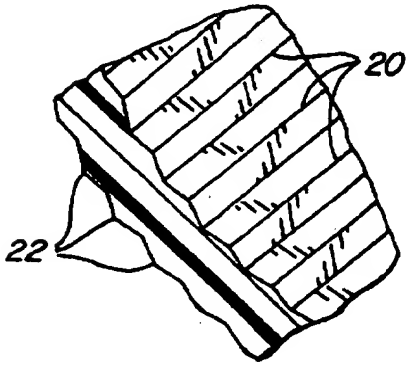


FIG. 2

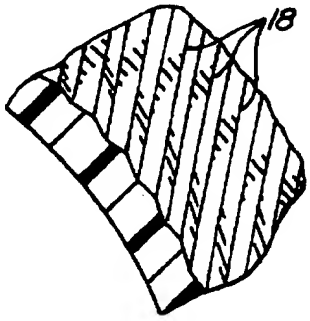


FIG. 3.

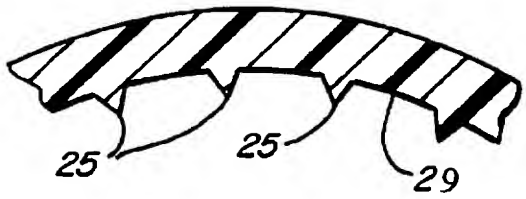


FIG. 3A.

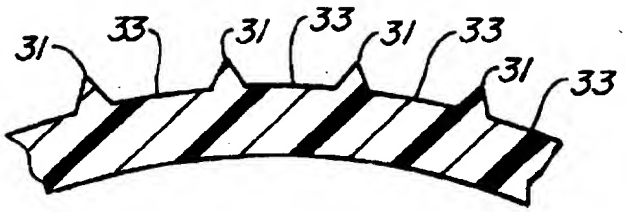


FIG. 3B.

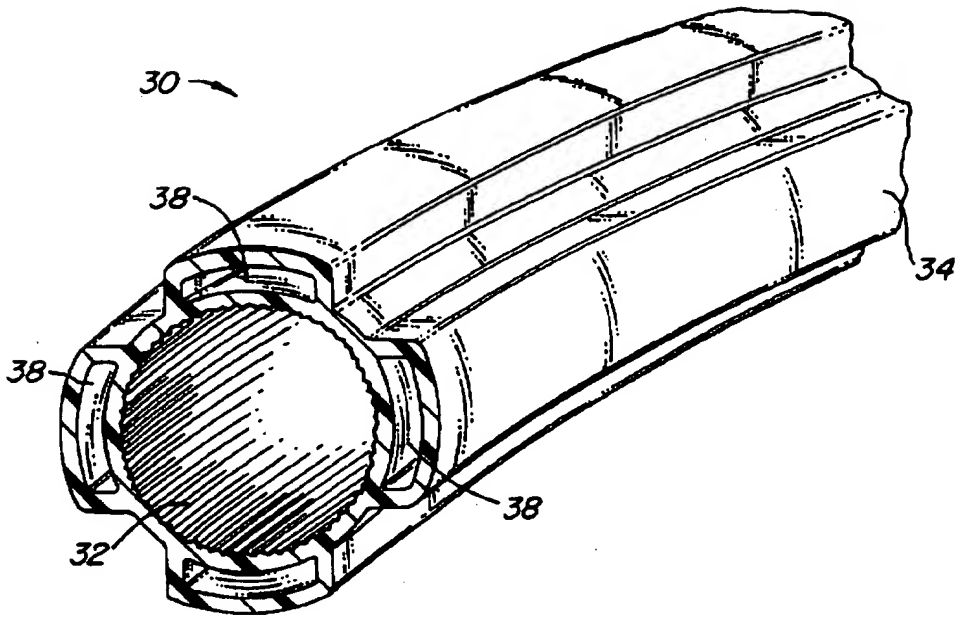


FIG. 4.

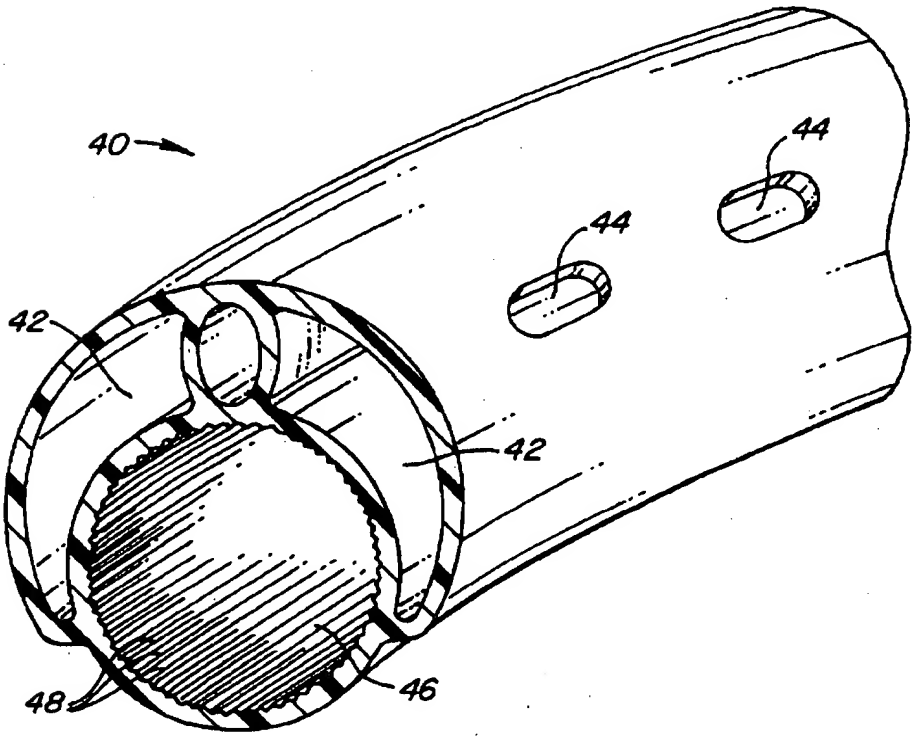


FIG. 5.

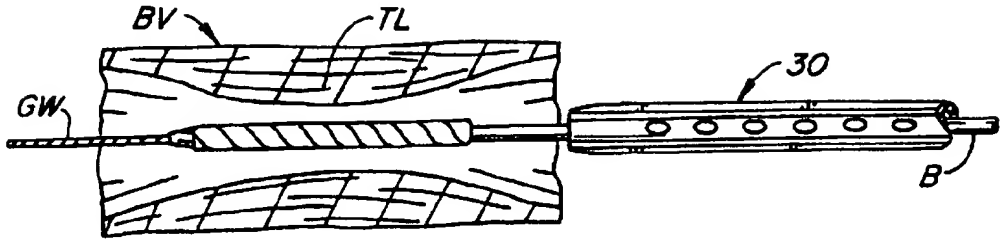


FIG. 6A.

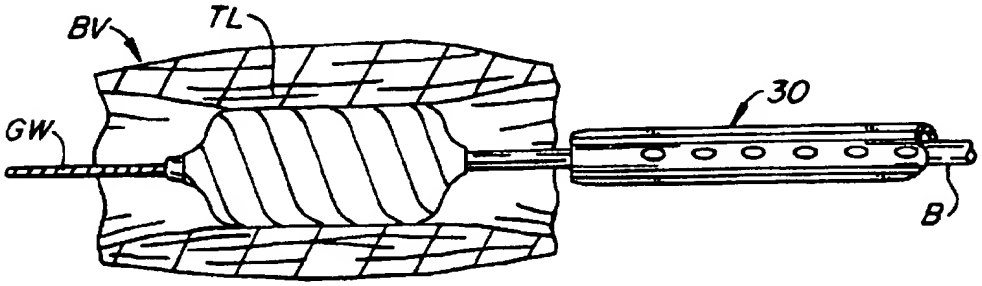


FIG. 6B.

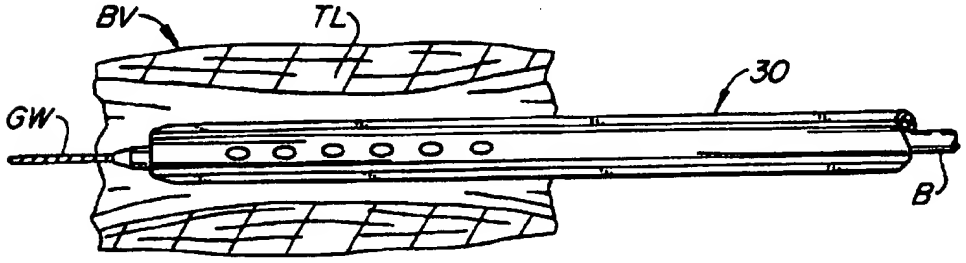


FIG. 6C.

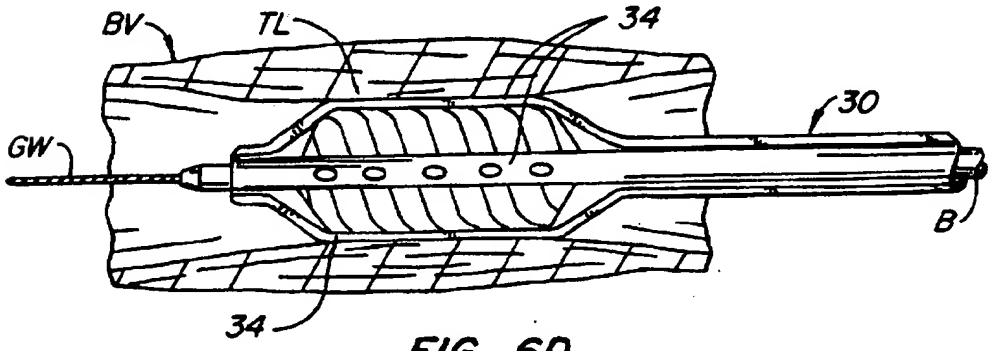


FIG. 6D.

METHOD AND SYSTEM FOR REDUCED FRICTION INTRODUCTION OF COAXIAL CATHETERS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to methods and devices for performing multiple, sequential intraluminal procedures. In particular, the present invention is related to a method and catheter system for reducing friction between coaxial catheters when they are axially translated relative to each other during the performance of such methods using such systems.

Intravascular and other intraluminal procedures frequently require the sequential introduction of two or more coaxial catheters, where each catheter provides a particular function or treatment modality which must be delivered to a common treatment location. For example, it has been proposed to treat atherosclerosis using two or more sequential procedures intended to address different parts of the overall therapy. Initial treatment often comprises angioplasty or atherectomy using a particular type of catheter followed by drug delivery, stent placement, perfusion, imaging, or the like, in order to further treat or assess the target location. Of particular interest to the present invention, systems and methods employing a base catheter for effecting the primary treatment and a sleeve catheter for effecting the secondary treatment or imaging have been proposed in copending application Ser. No. 08/222,143, assigned to the assignee of the present application, the full disclosure of which is incorporated herein by reference. Using such methods in coronary applications, the base catheter and sleeve catheter will usually be introduced together through a guiding catheter which extends from a primary percutaneous access site, such as a femoral access site in the groin, to a coronary ostium. The base catheter and sleeve catheter can be introduced through the guiding catheter to the target location within the coronary vasculature, and the two catheters then translated axially relative to each other to selectively or simultaneously position the working end of each catheter at the target location.

While a significant improvement over the use of separate catheters for each intended treatment or diagnostic protocol, such coaxial catheter systems suffer from the limited availability of lumen area in the guiding catheter. Because of the limited lumen area, the catheters must be made to be close fitting, with the sleeve catheter usually having a diameter which is no more than 10% to 25% greater than the outer diameter of the base catheter. Under such circumstances, friction between the inner lumenal surface of the sleeve catheter and the outer surface of the base catheter can be significant, rendering it difficult to axially position the catheters relative to one another after they have been deployed in the vasculature. Additionally, since the combination of sleeve catheter and base catheter will usually present a larger combined profile than a single-purpose catheter, there may be greater friction between the outer surface of the sleeve catheter and the inner surface of the guiding catheter during the initial introduction.

For these reasons, it would be desirable to provide improved methods for the intraluminal introduction of coaxial catheter systems where the friction between such catheters is reduced. If would be further desirable if the friction between the combined coaxial catheters and a third coaxial catheter, such as a coronary guiding catheter, is also reduced. It would be still further desirable to provide methods for fabricating tubular catheters having reduced surface friction when employed with coaxial catheters which are disposed either over or within a lumen of the tubular catheter. It would be still further desirable to provide a catheter system having a base catheter and a sleeve catheter, where the friction between the base catheter and the sleeve catheter is reduced to lower the force necessary to slide the catheters relative to each other.

2. Description of the Background Art

A guide wire having an extruded sleeve with an unsmooth surface is described in U.S. Pat. No. 5,404,887. An angioplasty catheter which may incorporate the design of U.S. Pat. No. 5,404,887 is sold by SciMed Life Systems, Inc., Minneapolis, Minn., under the trade name TRIO 14. A guiding catheter having channels on its interior surface resulting from inclusion of a spiraled reinforcement layer is shown in WO 93/23105. A catheter having an irregular outer or inner surface resulting from an embedded reinforcing member is described in WO 92/19308. Other catheter structures having projections or features on their interior and/or exterior surfaces are described in U.S. Pat. Nos. 5,217,440; 5,122,125; 5,054,501; and 1,596,754.

The construction and use of sleeve catheters for a variety of purposes are described in U.S. Pat. No. 5,336,178, and copending application Ser. Nos. 08/047,737; 08/222,143; 08/461,222 (FWC of 08/221,613); 08/305,250; and 08/401,541.

SUMMARY OF THE INVENTION

The method of the present invention for introducing a sleeve catheter over a base catheter comprises introducing a base catheter over a guide wire to a target location within a body lumen, usually a blood vessel, and more usually a coronary artery. The sleeve catheter is introduced coaxially over the base catheter to the target location, sometimes being pre-loaded and sometimes being post-loaded over the base catheters, and then being introduced simultaneously with the base catheter. At least one of the exterior surface of the base catheter and the interior surface of the sleeve catheter has an irregular surface which reduces friction between the sleeve catheter and the base catheter as they are axially translated relative to each other. Alternatively, both the exterior surface of the base catheter and the interior surface of the sleeve catheter will have irregular surfaces. Optionally, the base catheter and the sleeve catheter may be introduced through a guiding catheter, where the exterior surface of the sleeve catheter has an irregular surface in order to reduce sliding friction between the sleeve catheter and the guiding catheter. A preferred irregular surface is characterized by a continuous, circumferential pattern of V-shaped peaks, where the peaks are preferably circumferentially spaced-apart by an arc in the range from 6° to 24°. Such V-shaped peaks may be aligned axially (i.e., in a direction parallel to the axial direction of the catheter), as a spiral over the catheter, or in a zig-zag pattern over the catheter surface.

The present invention also provides a method for fabricating a tubular catheter having an irregular surface intended to reduce sliding friction when used with a coaxial catheter. The method comprises extruding a polymeric resin through an extrusion tool comprising an outer die and an inner pin. At least one of the die and pin is patterned to produce a repeatable pattern of surface irregularity as the tubular catheter is extruded through the tool. Optionally, both the pin and the die may be patterned to produce a tubular catheter having surface irregularities on both its inner (lumenal) and outer surfaces. Preferably, the die or pin

irregularities will comprise a continuous, circumferential pattern of V-shaped grooves which will impart a pattern of V-shaped peaks on the catheter surface as the extruded catheter material is drawn through the tool. While the arc between circumferentially spaced-apart grooves remains generally unchanged in the extrusion draw-down process that forms the peaks on the catheter surface, the die groove depth generally corresponds to a substantially diminished peak height in the extrusion since the radial features in the tool are drawn down pronouncedly during the extrusion process. Typically, a tool groove in the range from 0.1 mm to 1.0 mm can provide an extruded peak height in the range from 0.01 mm to 0.05 mm. The tubular catheter may be drawn without rotation through the extrusion tool which produces a pattern of linear, axially-aligned peaks on the catheter surface. Alternatively, the tubular catheter may be rotated continuously or intermittently as it is drawn through the extrusion tool, thus producing a spiral, zig-zag, serpentine, or other pattern of peaks on the catheter surface.

The present invention provides a second method for fabricating a tubular catheter having an irregular surface. In this method, a tubular catheter is first extruded, either in a conventional manner or in the manner just described for producing generally axially-aligned peaks on a catheter surface. Additional surface irregularities may be formed (or the initial surface irregularities maintained) by imprinting such irregularities onto a surface of the catheter after the extruding step. In particular, surface irregularities may be imprinted over the inner (lumenal) surface of the tubular catheter by positioning the extruded catheter body over a mandrel having a preselected pattern of surface irregularities (usually grooves or other cavities) and heating at least a portion of the catheter body to imprint the pattern from the mandrel onto the inner surface of the catheter. In order to form surface irregularities on the exterior surface of the catheter, the extruded catheter body is positioned in a mold having a preselected pattern of surface irregularities (again, typically grooves or other cavities), solid mandrel(s) are positioned in the lumen(s) of the catheter for support, and heating at least a portion of the catheter body to imprint the pattern from the mold onto the outer surface of the catheter.

The catheter system according to the present invention comprises a base catheter and a sleeve catheter. The base catheter has a proximal end, a distal end, and an interactive device near the distal end. The sleeve catheter has a proximal end, a distal end, an axial lumen, and an interactive device near the distal end. The axial lumen of the sleeve catheter receives the base catheter, in the manner generally described above, and at least the lumenal surface of the sleeve catheter includes surface irregularities to reduce surface friction between the base catheter and the sleeve catheter. Preferably, the surface irregularities comprise a plurality of V-shaped peaks, where the peaks are circumferentially spaced-apart by an arc in the range from 6° to 24°, and the peaks may be aligned axially, spirally, in a serpentine pattern, or in a zig-zag pattern.

The present invention still further provides sleeve catheters which are produced by the fabrication methods described above.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a perspective view of a portion of a catheter system constructed in accordance with the principles of the present invention and including an inner base catheter having an exterior grooved surface and an outer sleeve catheter having an exterior and an interior grooved surface.

FIG. 2 is a detailed view of a section of the outer sleeve catheter taken along line 2—2 of FIG. 1.

FIG. 3 is a detailed view of the inner base catheter taken along line 3—3 of FIG. 1.

FIGS. 3A and 3B show alternative low friction surfaces according to the present invention.

FIG. 4 is a perspective view of a drug delivery sleeve catheter constructed in accordance with the principles of the present invention.

FIG. 5 is a perspective view of a portion of a perfusion flow sleeve catheter constructed in accordance with the principles of the present invention.

FIGS. 6A–6D illustrate the method of catheter positioning of the present invention employing the drug infusion catheter of FIG. 4 deployed over a conventional angioplasty balloon catheter.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The present invention provides methods and devices for performing multiple, sequential intraluminal procedures on a patient as part of therapeutic or diagnostic treatment. By "intraluminal," it is meant that the procedures occur at a target location within a body lumen, usually being within the patient vasculature, more usually being within the arterial system, including the coronary arteries, the peripheral arteries, and the cerebral arteries. The methods and devices of the present invention, however, are not limited to use in the vascular system, and may also be advantageously employed in other body structures, including the prostate via the prostatic urethra, (e.g. to treat benign prostatic hypertrophy, prostatitis, and adenocarcinoma), the fallopian tubes via their lumens (to treat strictures), brain parenchyma (to treat Parkinson's disease), and the like.

The "target location" within the body lumen will usually be diseased or be suspected of being diseased. In the case of vascular treatment, the target locations will usually be stenotic regions where blood flow is restricted as a result of atheroma deposits or plaque. Diseased sites within other body lumens are well-known and described in the medical literature.

By "multiple" procedures, it is meant that at least two interventional and/or diagnostic, procedures will be performed as part of a single treatment regimen. Interventional procedures may also be referred to as therapeutic and include revascularization techniques, such as balloon angioplasty, laser angioplasty, ultrasonic angioplasty, atherectomy, and the like; drug delivery techniques; stent placement techniques; axial scoring or slitting of plaque prior to dilatation by balloon angioplasty; and the like. Diagnostic procedures include imaging particularly ultrasonic imaging but also including angioscopy, contrast delivery, and the like. By "sequential," it is meant that one procedure will be performed followed by performing another without having to exchange catheters over a guidewire, usually in any order, with or without repetitions. In the preferred case of intravascular treatment, at least one of the procedures will usually be therapeutic, more usually being balloon, laser or ultrasonic angioplasty, or atherectomy, while the other procedure may be therapeutic or diagnostic usually being drug delivery, perfusion, stent placement, pre-slitting of the plaque prior to angioplasty or imaging.

The methods of the present invention will utilize both a base catheter and a sleeve catheter which is slidably received

over the base catheter. Each of the base and sleeve catheters will include an interactive device at or near its distal end, and the catheters will usually be introduced together with the sleeve catheter being disposed over the base catheter. Once the distal ends of the catheters reach a location near the treatment site, the catheters may be axially translated relative to each other in order to sequentially or simultaneously position each interactive device at the treatment site. Conveniently, the base catheter can be a conventional therapeutic or diagnostic catheter usually being a therapeutic catheter more usually being an angioplasty catheter or an atherectomy catheter.

The sleeve catheter is sized to be received over the base catheter and provided with an interactive capability selected to complement or enhance the therapeutic capability of the base catheter. For example, it will frequently be advantageous to provide an imaging sleeve catheter with either an angioplasty or atherectomy base catheter, where the imaging capability can help assess the stenotic region prior and post treatment in order to provide more effective treatment. Drug delivery sleeve catheters are particularly useful to treat a target location after an angioplasty procedure in order to inhibit abrupt closure and restenosis. Perfusion sleeve catheters are ideally suited to provide blood flow distal to the target location when used in conjunction with conventional angioplasty balloon catheters during prolonged balloon inflation. Radially expandable sleeve catheters also permit carrying and subsequent placement of stents and grafts in combination with balloon angioplasty catheters. Alternatively, radially expandable sleeve catheters may carry cutting blades or other elements which may be deployed to score arterial plaque prior to balloon angioplasty.

The lumen of the sleeve catheter which receives the base catheter need not extend the entire length of the base catheter. Instead, a proximal portion of the sleeve catheter can consist essentially of a small diameter rod or tube, with an outside diameter typically in the range from 0.3 mm to 0.8 mm, which has sufficient flexibility to be introduced through the guiding catheter and the relatively non-tortuous regions of the vasculature but which has sufficient column strength to facilitate the axial translation of the sleeve catheter distal portion. For example, stainless steel hypotube can be used, where the lumen of the hypotube provides for fluid agent access in the case of a drug delivery device. The remaining description will be directed at embodiments where the sleeve body extends the entire length of the associated base catheter. It will be appreciated, however, that in at least some cases, a rod or narrow diameter tube can be substituted for the larger diameter tube body.

The design and construction of particular interactive devices is well-known and amply described in the patent and medical literature. For example, angioplasty devices and angioplasty catheters which may be used in the present invention are described in U.S. Pat. Nos. 5,041,089; 4,762,129; 4,775,371; 4,323,071, and 4,292,974, the full disclosures of which are incorporated herein by reference. Suitable atherectomy devices and catheters are described in U.S. Pat. Nos. 4,979,951; 5,071,425; Re. 33,569; 4,781,186; 4,926,858; 5,047,040; 5,181,920; 5,084,010; 5,226,909; 5,092,873; 5,222,966; 5,242,460; and 5,250,059, the full disclosures of which are incorporated herein by reference. Interventional laser angioplasty systems are commercially available from suppliers such as Trimedyne, Inc., Tustin, Calif., under the tradenames OPTILASE™, CARDIOLASE™ and LASERPROBE™. Interventional cardiovascular ultrasound systems for the destruction of plaque are described in U.S. Pat. Nos. 3,565,062 and 4,692,139, and WO 93/21835, the full disclosures of which are incorporated herein by reference, and Siegel et al. (1990) J. Am. Col. Cardiol. 15:345–351. Imaging devices suitable for use as the interactive device of the present invention will usually be ultrasonic, phased-array devices, such as described in U.S. Pat. Nos. 4,841,977 and 4,917,097, the full disclosures of which are incorporated herein by reference. Intravascular stents and stent delivery catheters are described in U.S. Pat. Nos. 4,776,337 and 5,092,877, the full disclosures of which are incorporated herein by reference.

According to the present invention, at least one of the sleeve catheter and the base catheter will have a surface modified to reduce friction between the base catheter and sleeve catheter when they are coaxially translated relative to each other. Optionally, the outer surface of the sleeve catheter may also have a modified surface in order to reduce friction when the sleeve catheter and base catheter are introduced through a guiding catheter. Thus, at least one of the outer surface of the base catheter and the inner surface of the sleeve catheter will be surface modified, and optionally the outer surface of the sleeve catheter will be further modified to reduce friction within the guiding catheter.

Surface modification according to the present invention comprises forming irregularities in the catheter wall so that contact area between the catheter wall and a second contact surface will be limited, thus reducing sliding friction. Such surface irregularities can take a variety of forms, including peaks, ridges, beads, pyramid patterns, waffle patterns, and other protrusions which limit contact area without interfering with free sliding of the coaxial catheters. Preferably, the irregularities will comprise a plurality of circumferentially spaced-apart peaks which extend longitudinally over at least a portion of the catheter body or bodies. Usually, the peaks will be axially aligned with each other, but they may also be arranged in spiral, serpentine, zig-zag, and other regular and irregular patterns. It will often be desirable to provide differing groove patterns on the inner surface of a sleeve catheter and outer surface of a base catheter, when the sleeve catheter and the base catheter are being used together in a catheter system. It will be appreciated that peak patterns having similar dimensions and mating geometries might have a tendency to lock with each other and prevent free relative axial translation of the catheters. Thus, by providing catheters with different surfaces (such as an axially-aligned peak pattern on one of the catheters and a spiral peak pattern on the other), contact area can be greatly minimized without the likelihood of locking between the groove patterns.

The preferred V-shaped peak pattern will comprise peaks which are circumferentially spaced apart by an arc in the range from 6° to 24°, preferably from 10° to 20°, and which have a peak height in the range from 0.01 mm to 0.05 mm, preferably from 0.015 mm to 0.02 mm. Specific methods for forming the peak patterns in the sleeve and base catheters are described hereinafter.

In a first preferred method for forming surface irregularities in the tubular catheter body, a polymeric resin is extruded through an extrusion tool comprising a die and a pin. At least one of the die and pin include a plurality of circumferentially spaced-apart V-shaped grooves which form the V-shaped peaks when the tubular body is extruded through the extrusion tool. It has been found that the V-grooves on the extrusion tool may be sized substantially greater than the desired dimensions of the V-shaped peaks on the catheter surface. Such surface features draw down more rapidly than the diameter or other major geometric features of the catheter body. Typically, it has been found

that when the major geometric features in the extrusion tool are sized typically four times greater than the desired dimensions of the catheter, the radial dimensions of the V-shaped grooves or other surface features in the extrusion tool must be sized from ten to twenty times greater than the desired radial dimension of the surface feature on the catheter, usually from twelve to eighteen times greater. Thus, for the exemplary major feature draw down ratio of four to one, for the V-shaped grooves, the groove depth on the tool will typically be in the range from 0.15 mm to 0.3 mm to produce a V-shaped peak on the catheter surface having a height of 0.015 mm.

Extrusion of the tubular catheters of the present invention will be formed in the generally conventional manner, except for the provision of the surface irregularities as described above. Thus, a polymeric resin will be provided and heated above its melting point prior to extrusion through the extrusion tool. Suitable polymeric resins include both natural and synthetic polymers, such as silicone rubber polyethylene, polyvinylchloride, polyurethanes, polyesters, polytetrafluoroethylenes (PTFEs), nylon, and the like. Optionally, the catheter sleeve body may be formed or co-extruded as a composite having one or more reinforcement layers incorporated within the polymeric body in order to enhance its strength, flexibility, pushability, and resistance to kinking. Additionally, the composition of the catheter body may vary along its length, with discrete portions of its length being composed from different materials and/or composites. Typically, the catheter body will be formed using extrusion techniques which are well described in the patent and medical literature.

As an alternative or an addition to formation of the surface features using specially shaped extrusion tools, as described above, surface features may be formed after extrusion process using suitable mandrels, molds, and the like. For example, surface features, such as axial peaks, may be formed over the interior luminal surface of the tubular catheter using a mandrel having axial grooves or other voids formed in its surface. The mandrel may be placed in the lumen, and the tubular catheter body thereafter heated and compressed in order to melt the surface so that material flows into the grooves or voids of the mandrel. In this way, the surface features defined by the mandrel may be imparted to the luminal surface of the tubular catheter. Similarly, external surface features can be imparted to the tubular catheter using a mold having axial grooves or other voids formed in its interior surface. When using a mold, it will often be desirable to support the lumens of the catheter body with solid mandrels. The mold, catheter, or both will be heated in order to at least partially melt the catheter body and form the desired features. Often, the tubular catheter will be formed using the extrusion process described above where features are formed by an extrusion tool having specialized geometry, where such surface features are maintained using specialized molds or mandrels as just described, following the loss of these surface features due to secondary processing, such as tipping, or the like.

Referring now to FIGS. 1–3, exemplary catheter system 10 comprising a base catheter 12 and a sleeve catheter 14 is illustrated. Base catheter 12 has a plurality of spiral peaks 18 formed over its outer surface, as best illustrated in FIG. 3. The inner surface of the base catheter 18 is smooth, but could optionally employ surface grooves or other irregularities.

The sleeve catheter 14 comprises a plurality of circumferentially spaced-apart peaks 20 over its inner luminal surface and 22 over its outer surface. By employing spiral peaks 18 on the base catheter 12 and axial peaks 20 on the sleeve catheter 14, the likelihood that the peaks of one will seize against the grooves between the peaks of the other is greatly diminished. Moreover, the total contact area between points of the catheters is greatly reduced to that of the crossing points of the contacting peaks, significantly diminishing the sliding friction therebetween. Even if the outer surface of the base catheter 12 were smooth, peaks 20 on the lumen of the sleeve catheter 14 would provide significantly reduced sliding friction therebetween when compared to the sliding friction between two smooth surfaces. By providing axial peaks 22 on the outer surface of the sleeve catheter 14, the combination of base catheter 12 and sleeve catheter 14 may be introduced through a conventional guiding catheter with reduced sliding friction.

Alternative configurations of low friction surface of the present invention are shown in FIGS. 3A and 3B. FIG. 3A shows peaks 25 circumferentially spaced-apart by a flat region 27 by flat regions 29 on an inner surface of a tubular member. Similarly, FIG. 3B shows peaks 31 spaced-apart by flat regions 33 on an outer surface of a tubular member. The peaks 25 and 31 could be formed into linear, spiral, serpentine, or any other pattern as discussed above.

Referring now to FIG. 4, drug delivery catheter 30 having an inner luminal surface 32 modified in accordance with the principles of the present invention will be described. Drug delivery catheter 30 is of the type described in copending application Ser. No. 08/241,428, the full disclosure of which is incorporated herein by reference. Four drug infusion tubes 34, are formed over the exterior surface of the catheter 30. A liquid medium carrying a desired therapeutic agent may be delivered through perfusion lumens 38 of each infusion tube 34. The V-shaped peaks formed over the inner luminal surface will reduce surface friction as the drug infusion catheter 30 is introduced over a conventional balloon catheter, as described in more detail below in connection with FIGS. 6A–6D.

A blood perfusion catheter 40 is illustrated in FIG. 5. Catheter 40 includes a pair of perfusion lumens 42 having perfusion ports 44 formed in the wall thereof. Catheter 40 may be disposed over a balloon or other catheter in order to provide for blood perfusion through the lumens 42. A central lumen 46 is provided for receiving the balloon or other catheter, which lumen 46 includes the V-shaped peaks 48 of the present invention. Construction of such perfusion catheters (without surface irregularities formed on the catheter-receiving lumen thereof) is described in copending application Ser. No. 08/461,222 (FWC of 08/221,613), the full disclosure of which is incorporated herein by reference.

Referring now to FIGS. 6A–6D, a drug infusion catheter 30 may be positioned over a balloon catheter B and introduced to a target location TL in a blood vessel BV over a guide wire GW in a generally conventional manner. After the balloon catheter B is positioned at the target location, as shown in FIG. 6A, the balloon will be inflated to dilate the target location, as shown in FIG. 6B. The drug delivery catheter 30 will remain proximal to the balloon during the balloon inflation.

After achieving the desired dilatation, the balloon is deflated, and the drug infusion catheter advanced distally, as shown in FIG. 6C. The low friction surface of the inner lumen of the drug delivery catheter 30 facilitates such distal advancement and allows precise positioning of the catheter 30 over the balloon.

After positioning has been achieved, the balloon of balloon catheter B is again inflated, engaging drug infusion

tubes 34 of the drug delivery catheter 30 against the wall of the blood vessel BV. The drug may then be delivered directly into the blood vessel wall through the drug infusion tubes 34.

Although the foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

What is claimed is:

1. A method for introducing a sleeve catheter over a base catheter into a body lumen, said method comprising:

introducing the base catheter over a guide wire to a target location within the body lumen, and

translating the sleeve catheter coaxially over the base catheter while said base catheter is positioned within the body lumen, wherein the base catheter and the sleeve catheter are introduced coaxially through a guiding catheter;

wherein at least a distal portion of the exterior surface of the base catheter and a distal portion of the interior surface of the sleeve catheter have irregular surfaces to reduce friction and wherein the pattern of surface irregularities on the base catheter is selected so that it will not mate with the pattern of surface irregularities on the sleeve catheter.

2. The method as in claim 1, wherein one of the patterns comprises spiral peaks and the other comprises axial peaks.

3. The method as in claim 1, wherein an exterior surface of the sleeve catheter has an irregular surface to reduce sliding friction with the guiding catheter.

4. The method as in claim 1, wherein the irregular surface is characterized by a continuous circumferential pattern of V-shaped peaks.

5. The method as in claim 4, wherein the V-shaped peaks are circumferentially spaced-apart by an arc in the range from 6° to 24°.

6. The method as in claim 5, wherein the V-shaped peaks are aligned in a pattern selected from the group consisting of axial, spiral, and zig-zag.

7. A method for fabricating a tubular catheter having an irregular surface, said method comprising

extruding a polymeric resin through an extrusion tool comprising an outer die and an inner pin, wherein at least one of the die and the pin is patterned to produce a repeatable pattern of surface irregularities as the tubular catheter is extruded through said tool, wherein said surface irregularities reduce sliding friction between said tubular catheter and another catheter which is introduced over or through said tubular catheter and which engages the surface with said surface irregularities.

8. The method as in claim 7, wherein both the pin and die are patterned to produce a tubular catheter having inner and outer surfaces with surface irregularities on said inner and outer surfaces.

9. The method as in claim 7, wherein a surface of the die or pin comprises a continuous circumferential pattern of V-shaped grooves which will impart a pattern of V-shaped peaks on the outer or inner surface of the catheter, respectively.

10. The method as in claim 9, wherein the grooves are circumferentially spaced-apart by an arc in the range from 6° to 24°.

11. The method as in claim 10, wherein the grooves have a depth in the range from about 0.1 mm to 1 mm which will impart a drawn down peak height in the range from 0.01 mm to 0.05 mm.

12. The method as in claim 9, wherein the tubular catheter is drawn without rotation through the extrusion tool to produce linear peaks on the catheter.

13. The method as in claim 9, wherein the tubular catheter is rotated as the tubular catheter is drawn through the extrusion tool to produce a spiral or zig-zag peak pattern on the catheter surface.

* * * * *

US005843172A

United States Patent [19]

Yan

[11] Patent Number: 5,843,172

[45] Date of Patent: Dec. 1, 1998

[54] **POROUS MEDICATED STENT**

[75] Inventor: **John Y. Yan**, Los Gatos, Calif.

[73] Assignee: **Advanced Cardiovascular Systems, Inc.**, Santa Clara, Calif.

[21] Appl. No.: **842,660**

[22] Filed: **Apr. 15, 1997**

[51] **Int. Cl.**[6] **A61F 2/06**

[52] **U.S. Cl.** **623/1**; 623/2; 606/198; 606/191; 604/104

[58] **Field of Search** 623/1, 2, 12; 606/191, 606/195, 198, 153; 604/104, 107

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,855,638	12/1974	Pilliar	623/16
4,101,984	7/1978	MacGregor	623/2
4,355,426	10/1982	MacGregor	623/1
5,163,958	11/1992	Pinchuk .	
5,370,684	12/1994	Vallana et al. .	
5,419,760	5/1995	Narciso, Jr.	623/12
5,441,515	8/1995	Khosravi et al.	623/12
5,571,187	11/1996	Devanathan	623/16
5,624,411	4/1997	Tuch .	
5,630,840	5/1997	Mayer .	
5,632,779	5/1997	Davidson .	
5,697,967	12/1997	Dinh et al.	623/1
5,707,385	1/1998	Williams	604/104
5,725,567	3/1998	Wolff et al.	623/1

FOREIGN PATENT DOCUMENTS

WO 95/11817 5/1995 WIPO .

WO 96/28115 9/1996 WIPO .

OTHER PUBLICATIONS

Lambert, Thomas L., M.D., et al., Localized Arterial Wall Drug Delivery From a Polymer-Coated Removable Metallic Stent, *Circulation*, Eol. 90, No. 2 (Aug. 1994) pp. 1003–1011.

De Scheerder, Ivan K, et al., Biocompatibility of Polymer-Coated Oversized Metallic Stents Implanted in Normal Porcine Coronary Arteries, *Atherosclerosis*, vol. 114 (1995), pp. 105–114.

Primary Examiner—Paul B. Prebilic

Attorney, Agent, or Firm—Fulwider Patton Lee & Utecht, LLP

[57] **ABSTRACT**

A medicated prosthesis, such as a stent, is deployed in a human vessel. A metallic stent has a plurality of pores in the metal which are loaded with medication. When the stent is implanted into the vasculature of a patient, the medication in the stent dissipates into the tissue of the vasculature proximate the stent. The stent may be formed from a porous metal in the form of a wire, tube, or metal sheet. The present invention also includes a method of treating vasculature disease by delivering medication to the site of the vascular disease including the step of deploying a metal stent having a plurality of pores in the stent and further having medication in the pores and delivering the stent to the site of vasculature disease.

27 Claims, 5 Drawing Sheets

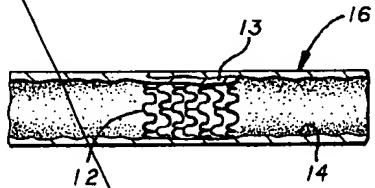
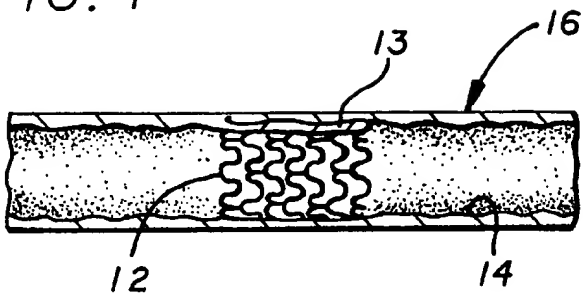


FIG. 1



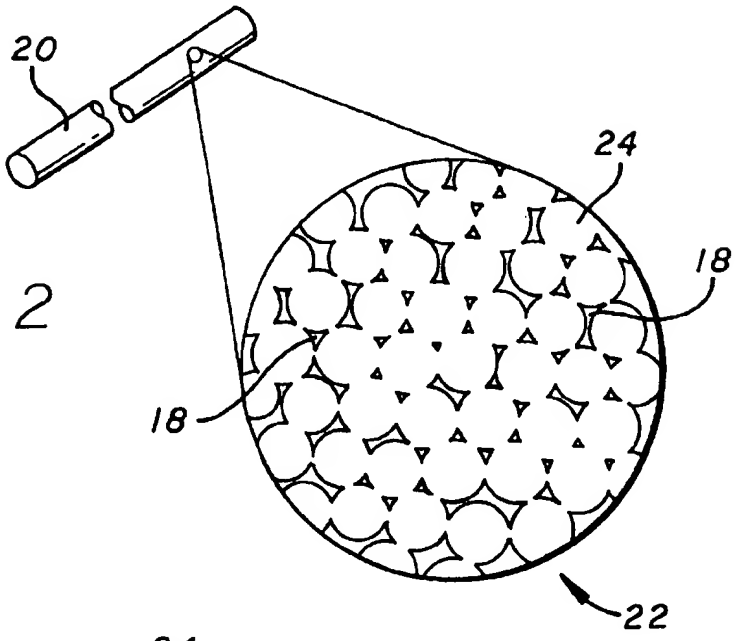


FIG. 2

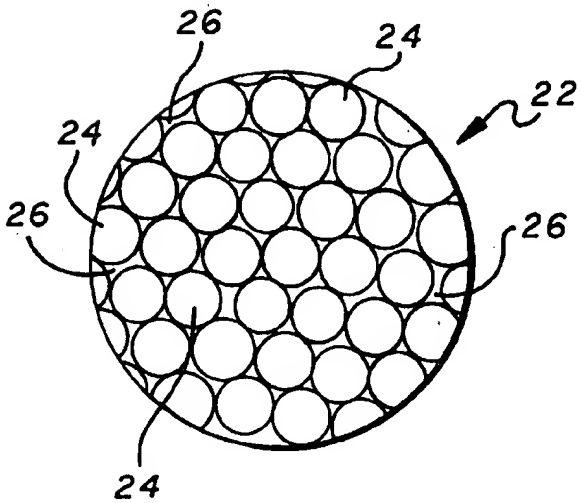
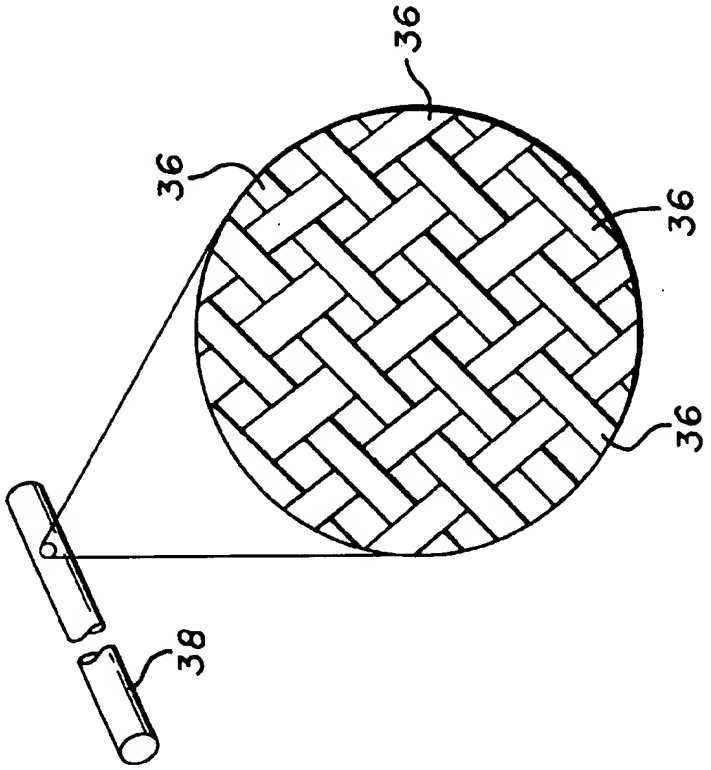


FIG. 3

FIG. 5



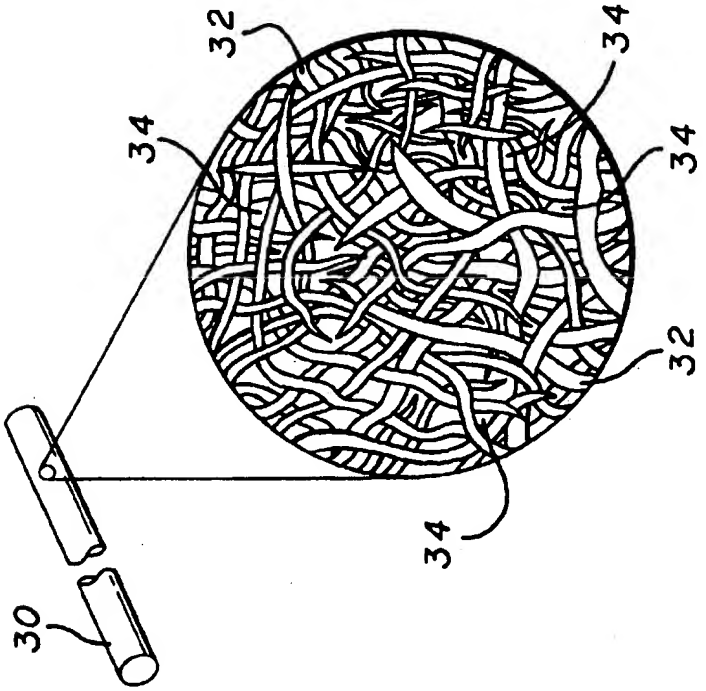


FIG. 4

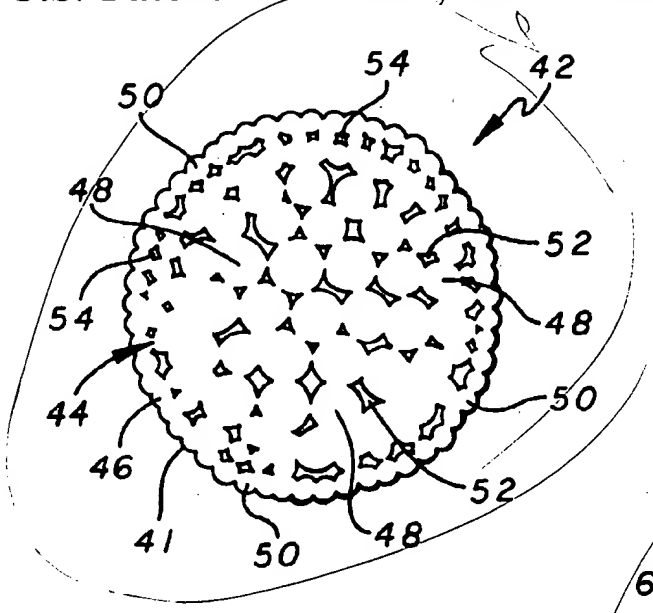


FIG. 6

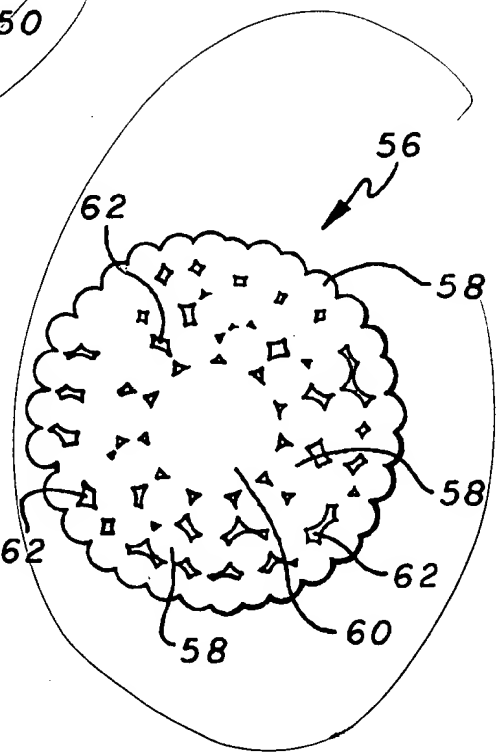


FIG. 7

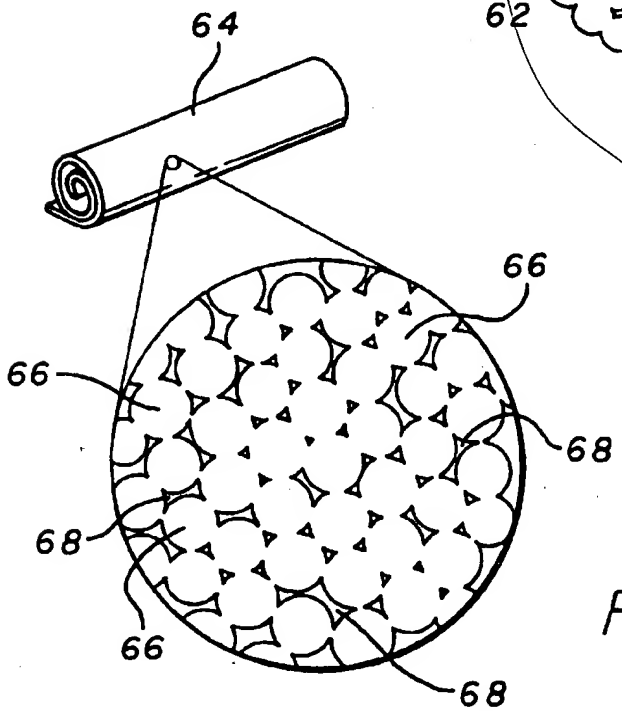
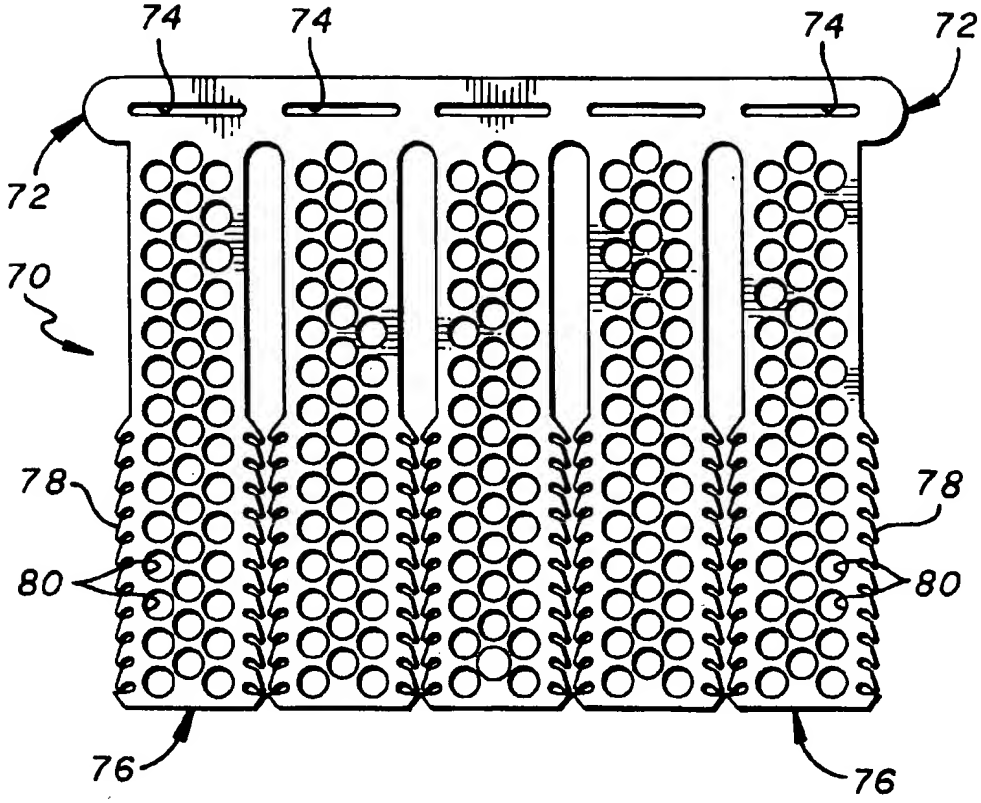


FIG. 8

FIG. 9


74
74
74
72
72
70
78
78
80
80
76
76

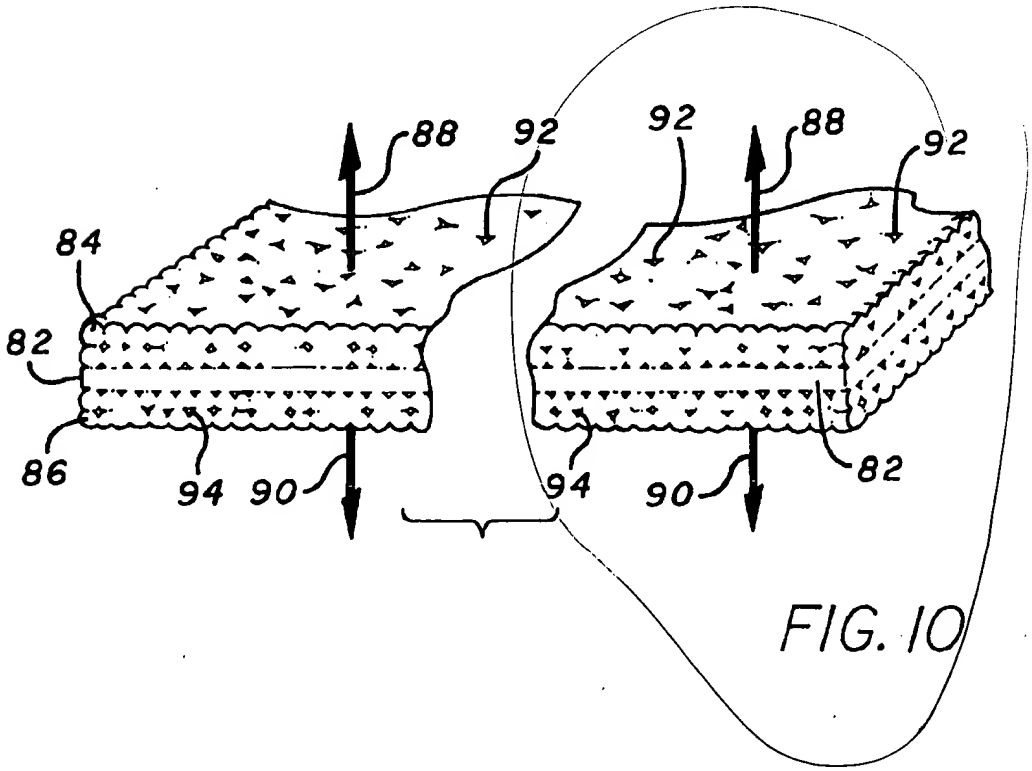

88
92
92
88
92
84
82
86
94
90
94
90
82

FIG. 10

FIG. 11

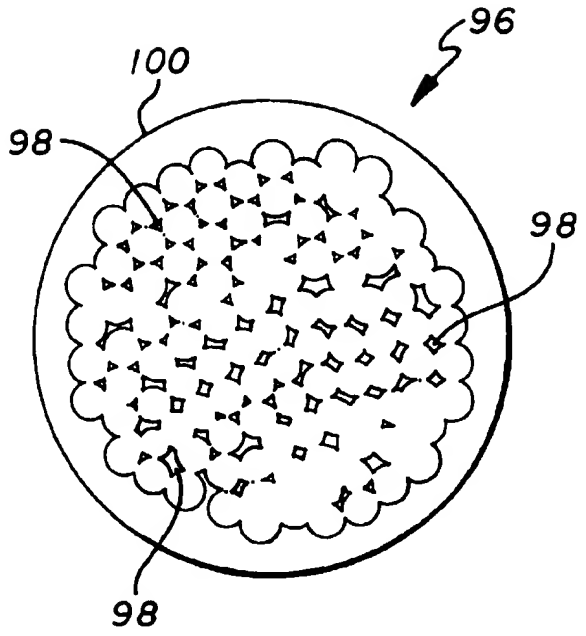
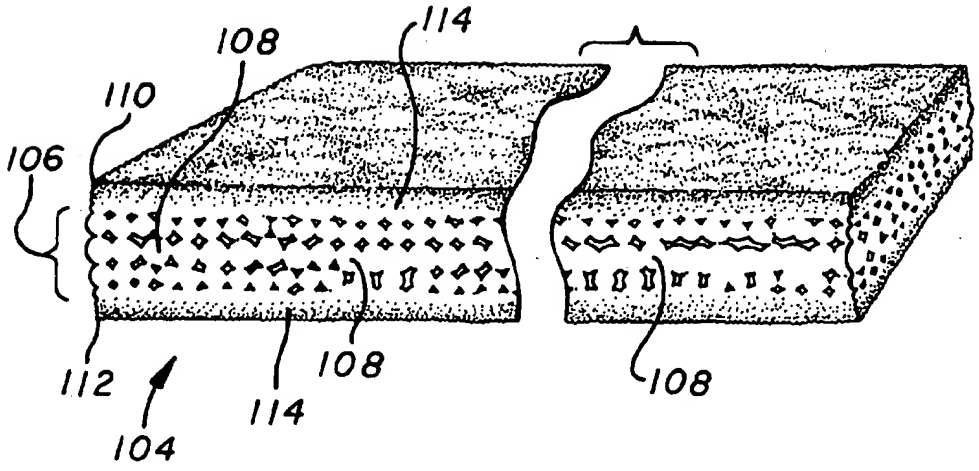


FIG. 12



POROUS MEDICATED STENT

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention generally relates to a medicated prosthesis or implant. More particularly, the invention relates to a medicated intra-vascular prosthesis, such as a stent, that is radially expandable in the vasculature of a patient and delivers a therapeutic agent to the site of the implantation.

2. Description of Related Art

Stents are generally cylindrically shaped prosthetic implants which function to hold open and sometimes expand a segment of a blood vessel or other anatomical lumen. They are particularly suitable for supporting and preventing a torn or injured arterial lining from occluding a fluid passageway. Intravascular stents are increasingly useful for treatment of coronary artery stenoses, and for reducing the likelihood of the development of restenosis or closure after balloon angioplasty.

The success of a stent can be assessed by evaluating a number of factors, such as thrombosis; neointimal hyperplasia, smooth muscle cell migration and proliferation following implantation of the stent; injury to the artery wall; overall loss of luminal patency; stent diameter in vivo; thickness of the stent; and leukocyte adhesion to the luminal lining of stented arteries. However, the chief areas of concern are early subacute thrombosis, and eventual restenosis of the blood vessel due to intimal hyperplasia.

Therapeutic pharmacological agents have been developed to improve successful placement of the stent and are delivered to the site of stent implantation. Stents that are of a common metallic structure were previously unable to deliver localized therapeutic pharmacological agents to a blood vessel at the location being treated with the stent. There are polymeric materials that can be loaded with and release therapeutic agents including drugs or other pharmacological treatments which can be used for drug delivery. However, these polymeric materials may not fulfill the structural and mechanical requirements of a stent, especially when the polymeric materials are loaded with a drug, since drug loading of a polymeric material can significantly reduce the structural and mechanical properties of the polymeric material.

It has been known in the art to coat a metallic stent with a polymeric material and load the polymeric material with a drug. Alternatively stents of polymeric materials have been reinforced with metal structure. These stent designs have the strength necessary to hold open the lumen of the vessel because of the reinforced strength of the metal. Stents made of both polymeric material and metal have a larger radial profile because the volume occupied by the metal portion of the stent cannot absorb and retain drugs. Reducing the profile of a stent is preferable because it increases the in vivo diameter of the lumen created by the stent. Thus it is desirable to configure a metallic stent to deliver drugs to the blood vessel walls without substantially increasing the profile of the stent. The present invention meets these needs.

SUMMARY OF THE INVENTION

Briefly, and in general terms, the present invention provides for an implantable prosthesis that is made of metal and has porous cavities in the metallic portion of the prothesis so that the drugs can be loaded directly into the pores without substantially weakening the structural and mechanical characteristics of the prosthesis. The stent of one embodiment of the present invention can be implanted in the specific site of vascular injury such as can occur from balloon angioplasty or de novo lesions of a therosclerotic disease. The drugs in the pores of the stent can treat restenosis, tissue inflammation, promote endothelialization or any other disease that may inhibit the successful implantation of a stent.

In one embodiment of the invention, the porous cavities of the stent can be formed by sintering the stent material from metallic particles, filaments, fibers or other materials. The stent can be formed from a sintered wire that is coiled or otherwise formed into a stent. The stent can be formed from a sintered cylindrical tube or sintered metal sheet which can be laser cut or chemical etched into an expandable stent structure.

Additionally, the porosity of the stent metal can be increased by using particles that are not spherical such as fibrous particles, filaments or wires. In one embodiment of the invention, the interwoven fibers and filaments can also be sintered after they are woven into the desired shape.

In one embodiment of the present invention, the stent is formed from a metal wire or strut that is formed of a first layer of particles oriented along an axis forming a core and an outer layer of particles arranged radially outward from the inner layer of particles. The outer layer of particles has a smaller diameter than the inner layer of particles. This embodiment has the advantage that the stent can hold more of the drugs in the center of the stent. The smaller diameter particles on the outside controls the rate at which drugs are released into the walls of the vessel. The larger diameter particles create cavities of greater porosity to hold a larger volume of medication.

In another embodiment it may be desirable to form a stent having a solid core and a porous outer section. This can be accomplished by sintering particles to a solid non-porous metal wire. A stent so configured has a solid core which reinforces the structure of the stent. The porous particles sintered to the surface of the stent absorb drugs for delivery.

In one embodiment according to the present invention, the stent is formed from a sheet or tube of sintered metal. The sheet or tube is cut according to a pattern that allows the stent to be expanded and deployed into the vasculature. The stent pattern of this embodiment can be stenciled onto the sheet or tube of sintered metal and then may be cut by laser cutting the sheet into the desired shape. Alternatively, the stent can be chemical etched into its desired shape.

According to another embodiment of the invention, the stent receives a coating on the surface of the stent. In certain applications, it is desirable that the coating be a bio-polymer and in other applications, the coating preferably is a synthetic polymer or a hydrogel. The coating can also be a heparin coating that is affixed to the surface of the stent through ionic bonding, end point attaching or photolinking the heparin.

The coating is preferably permeable to the medication according to one embodiment of the invention. The permeability of the coating should be selected to release the medication in the stent at a desired rate. In another embodiment of the present invention, a bioabsorbable coating is applied to the stent. This coating is dissolved by the body fluids. Furthermore, it is desirable in certain applications to load medication into the coating applied to the stent. The coating, according to one application is preferably the same drug or medication that is loaded into the stent in one embodiment. In other embodiment, the coating is loaded with a different medication. In this configuration, two medications are released in a sequential manner.

The present invention also includes a method of using a medicated prosthesis. The method comprises of providing a porous prosthesis, loading a drug into the porous cavity of the prosthesis, positioning the prosthesis in an appropriate site and affixing the prosthesis to the site. In another embodiment, the metal further includes the step of applying a coating to the stent after the step of loading the drug into the porous cavities of the stent.

These and other features of the present invention will become apparent from the following more detailed description, when taken in conjunction with the accompanying drawings which illustrate, by way of example, the principles of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a longitudinal sectional view of a blood vessel with stent manufactured according to one embodiment of the present invention.

FIG. **2** is a porous stent wire or strut in a partially magnified, partially cut away perspective manufactured according to one embodiment of the present invention.

FIG. **3** is a magnified, cross-sectional view of unsintered packed particle.

FIG. **4** is a porous stent wire or strut in partially magnified, partially cut away perspective manufactured according to one embodiment of the present invention.

FIG. **5** is a porous stent wire or strut in partially magnified, partially cut away perspective manufactured according to one embodiment of the present invention.

FIG. **6** is a cross-sectional view of a stent wire or strut manufactured according to one embodiment of the present invention.

FIG. **7** is a cross-sectional view of a stent wire or strut manufactured according to one embodiment of the present invention.

FIG. **8** is a sheet of sintered stent manufactured according to one embodiment of the present invention.

FIG. **9** is a stent formed from a sheet of sintered metal according to one embodiment of the present invention.

FIG. **10** is a cross-sectional, partially cut away view of a sheet of sintered metal manufactured according to the principles of one embodiment of the present invention.

FIG. **11** is a cross-sectional view of a stent wire or strut manufactured according to the principles of one embodiment of the present invention.

FIG. **12** is a cross-sectional view, partially cut away of a sheet of sintered metal manufactured according to the principles of one embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring now to FIG. **1**, the prosthesis of one embodiment is a porous stent **12** that is radially expandable against the walls **14** of a vessel **16**. The stent is loaded with a therapeutic agent in the pores (**18** of FIG. **2**) of the stent. When placed in the vasculature, the therapeutic agent is delivered to the tissue that comes into contact with the stent. The stent of one preferred embodiment is formed of a stent wire that is porous. An example of a porous stent wire is a sintered metal wire. FIG. **2** illustrates a partial microscopic view of a sintered wire that is suitable for use in one embodiment of the present invention. The wire is porous and has several porous cavities **18**. The size of the cavities preferably range between 0.01 and 20 microns in size.

Porous metal is made, according to one preferred embodiment, by the process of sintering metal. Sintering is a process of fabrication where particles are bonded together without entirely melting the particles. Particles are pressed together or molded into a desired shape. A considerable amount of pressure is first applied to press the particles together. Then, the metal is heated to temperatures slightly below the melting point of the metal. Without entirely melting, the particles bond to each other at their respective surfaces. Space remains between the lattice of the particles which define the porous cavities **18**.

The formation of sintered metal is illustrated with reference to FIG. **3** and continued reference to FIG. **2**. FIG. **3** is a microscopic view of a packed lattice **22** of metallic particles **24**. Gaps **26** exist between each particle despite the fact that the particles are pressurized and are in contact with adjacent particles. Particles are preferably sized between 0.02 microns and 20 microns in diameter. Prior to heating, there are no chemical bonds formed between the individual particles. When the metal is heated to slightly below the melting point of the metal, the particles bond with neighboring particles. The gaps in the packed lattice form pores **18** when the particles are sintered. Thus in FIG. **2**, the metal stent wire formed by the process of sintering has porous cavities **18** extending throughout the entire wire, thereby interconnecting the cavities. The cavities then can be filled with a therapeutic agent as hereinafter described. The appropriate pressure and temperature of sintering a particular metal is specific to that particular metal. One skilled in the art of metal fabrication would understand how to sinter any given metal or alloy.

For each of the embodiments, the metal stent material member can be a suitable metal such as stainless steel, tantalum, nickel-titanium alloy, platinum-iridium alloy, molybdenum-rhenium alloy, gold, magnesium, combinations thereof, although other similar materials also may be suitable. The metal can be modified to exhibit different hardnesses, and thus varying stiffnesses, by well known annealing and manufacturing processes.

One of the most important factors to be considered when making a stent according to one embodiment of the present invention is the porosity of the metal. Porosity is the total volume of pores in the sintered metal divided by the total volume of the metal. Porosity determines the amount of a therapeutic agent that can be loaded into a stent of predetermined dimensions. High porosity means that a stent can deliver more therapeutic agents or have a narrower profile because it is less dense. High porosity, according to some embodiments of the present invention, adversely affects the strength and elasticity of a metal. Consequently, there is an ongoing tradeoff between stent strength, on the one hand, and stent profile and stent load capacity on the other hand.

Pore size is a function of particle size and dimension. In one embodiment of the present invention illustrated in FIG. **3**, the particles **24** are generally spherical. Size of the pore **18**, particularly with generally spherical particles, is proportional to particle size. When the particles **24** have inconsistent size, smaller particles tend to fill the gaps between the larger particles. Thus, the porosity of such particles are less predictable. Consistent pore size is also important to ensure that drugs are evenly distributed throughout the stent. Consistent distribution on the other hand ensures that the tissue in contact with the stent will receive an even distribution of a therapeutic agent.

There are several types of drugs that are currently administered at the site that a stent is placed in the vessel.

Examples of therapeutic drugs, or agents that can be combined with the polymeric layers include antiplatelets, anticoagulants, antifibrins, antithrombins, and antiproliferatives. Examples of antiplatelets, anticoagulants, antifibrins, and antithrombins include but are not limited to sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antibody, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocore). Examples of cytostatic or antiproliferative agents include angiopeptin (a somatostatin analogue from Ibsen), angiotensin converting enzyme inhibitors such as Captopril® (available from Squibb), Cilazapril® (available from Hoffman-LaRoche), or Lisinopril® (available from Merck); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, Lovastatin® (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck), methotrexate, monoclonal antibodies (such as to PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available from Glazo), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic drugs or agents which may be appropriate include alpha-interferon and genetically engineered epithelial cells, for example.

While the foregoing therapeutic agents have been used to prevent or treat restenosis, they are provided by way of example and are not meant to be limiting, since other therapeutic drugs may be developed which are equally applicable for use with the present invention. The treatment of diseases using the above therapeutic agent are known in the art. Furthermore, the calculation of dosages, dosage rates and appropriate duration of treatment are previously known in the art.

The therapeutic agent of one embodiment is preferably in liquid form and is loaded into a stent by immersing the stent in a medicated solution. The therapeutic agent may be dissolved in a solvent or suspended in a liquid mixture. If a suspension of drugs are used, it is important that the pore size of the stent is considerably larger than the therapeutic agent. An average pore size that is more than ten (10) times the particle size of a suspended therapeutic agent is suitable. After the stent is emersed in the medicated solution, the therapeutic agent absorbs into the pores of the stent. At which time, the loaded stent can be removed from the solution and implanted into the vasculature of a patient. Additionally, a therapeutic agent can be loaded into the stent by applying pressure to the fluid to aid the passage of medicated fluid into the porous cavities of the stent. This can be done similar to how fluid can be pressurized through the pores of a filter.

Once loaded, the therapeutic agent remains in place by the surface tension between the walls **28** of the several porous cavities **18** and the therapeutic agent. As shown in FIG. **1**, the loaded or medicated stent **12** is then deployed to the site of arterial closure **13** and is expanded. The expanded stent engages the walls **14** of the vessel **16** to maintain the patency of the vessel. Once in the vessel, the therapeutic agent disseminates from the porous cavities **18**, as depicted in FIG. **2**, of the stent and is absorbed into the tissue of the walls of the vessel that are in contact with the stent.

The advantage of the stent of the present invention over prior art medicated stents is one of profile and strength. Metal, including sintered metal, is stronger than synthetic materials that are capable of being loaded with a therapeutic agent. Thus, in order for a medicated stent to deliver an appropriate amount of a therapeutic agent and structurally maintain vessel patency, the profile of the stent must be substantially larger than metal stents. This is true whether a metal stent is coated with a therapeutic agent, or if the stent is entirely made of a plastic material.

Sintered metal has strength and elasticity that is comparable to regular metal. Sintered metal furthermore has the added feature that it is porous. Consequently, a sintered stent can be made having a profile that is substantially comparable to a conventional metal stent. Yet, a therapeutic agent can be loaded into the pores and delivered to the site of stent implantation without the aid of medicated coatings.

Additionally, many synthetic materials, including materials that are bioabsorbable, cause inflammation of the tissue. A medicated stent that has a therapeutic agent loaded directly into the pores of the stent can avoid synthetic coatings that have been known to cause irritation at the site of stent implantation.

FIG. **4** illustrates an alternative embodiment of a stent wire **30** constructed according to the present invention. The stent is formed of elongated particles **32**, i.e., filaments and fibers. Sintered particles (**24** of FIG. **2**) that are generally spherical in shape are capable of forming sintered metal having a porosity in the range of 0.30 to 0.05. However, when filaments or fibers **32** are sintered, the porosity can be increased above 0.30. The technique of fabricating a stent with elongated filaments or fibers are similar to the method described above for spherical particles or powders. The filaments or fibers are molded and pressurized. Then the fibers are heated to a temperature just below the melting point of the metal.

Greater porosity of a stent made of metal filaments or fibers **32** rather than spherical particles (**24** of FIG. **2**) is obtained because of the irregular shape of the particles. The particles cannot be packed as tightly as regular generally spherical particles. Furthermore, the particles can be packed less densely and still maintain contact between the particles to allow sintering. Thus, the void space or pores **34** in the sintered metal are larger.

The strength of a stent wire **30** using filaments in FIG. **4** is improved because the individual strands have larger surface area to volume and contact a greater number of neighboring strands. Thus, each filament or fiber will have a larger bonding surface and may bond with a greater number of neighboring fibers. A matrix of overlapping filaments or fibers is thus formed with greater porosity and stronger inter-particle bonding.

In yet another embodiment, wire fibers **36** are woven or twined into a structure **38** as illustrated in FIG. **5**. The individual strands cooperate in a synergistic manner to reinforce the strength of the wire. Additionally, the wire fibers can be woven into the form of a sintered metal sheet having improved and reinforced strength or a sintered metal tube. Other combinations of particle size and shape can be employed to form a stent wire having different characteristics.

In another embodiment illustrated in FIG. **6**, the stent wire **42** is formed of an inner core **44** and an outer layer **41** of sintered particles. The outer layer is formed from articles having a different diameter than the diameter of the particles that form the inner core. For example, the core of the metal is formed of particles that have a diameter in the range of 10–20 microns at the core of the wire. Surrounding the core

are particles that have a diameter in the range of 2–4 microns on the outer surface. The larger particles create a core having larger pores **52**. This results in higher porosity and thus a higher load capacity. The smaller particles on the outer layer form smaller pores **54** which reduce the rate of diffusion of drugs into the tissue of the vessel.

When a therapeutic agent is loaded into a stent formed of the stent wire **42** illustrated in FIG. **6** a larger volume can be stored in the larger pores **52** at the core **44** of the stent wire. Once the stent is placed into the vessel, the therapeutic agent in the stent wire is delivered at a rate determined by the smaller pores **54** in the outer layer **46** of the stent wire. Such a structure is expected to have a benefit of being able to store a large amount of therapeutic agent at the core and deliver the therapeutic agent at a slower rate. Consequently, this design is desirable for low-dose, long-term drug therapy.

Alternatively, according to another embodiment of the present invention shown in FIG. **7**, a stent wire **56** is formed from sintered particles **58**. The pores **62** formed between the sintered metal particle surrounding the solid core retain the therapeutic agent. The total porosity of a stent having a solid core and porous outer layer is much lower than a stent wire of similar proportion that is entirely made of sintered particles. However, the solid core reinforces the tensile strength and elasticity of the metal stent and is considerably stronger. Thus, it is desirable to use a sintered stent with a solid core for applications where maximum tensile strength and elasticity is desirable and only a relatively small amount of therapeutic agent is needed.

The sintered metal stent of yet another embodiment of the present invention can be made of material formed in different shapes than sintered metal. For example, the stent can be formed of a sheet of sintered metal as shown in FIG. **8** or a sintered metal tube. By way of example, metal particles **66** are arranged and pressurized into a sheet. The sheet is heated to a temperature below the melting point of the particles as described previously. The sheet of sintered metal is porous and has a plurality of pores **68**.

The same principles that apply to porosity and pore size of a wire apply equally to a sintered stent that is formed into a sheet or tube. The advantage of forming the stent from a sheet of metal is that the stent is radially expandable without placing a great deal of strain on the metal lattice when it is expanded. A sheet or tube of sintered metal can be cut in the desired shape to form the metal structural member with a laser, such as a continuous CO_2 laser, a pulsed YAG laser, or an excimer laser, for example, or alternatively, by chemical etching or stamping. When cut from a flat sheet, the stent is then rolled into a cylindrical configuration and laser welded along the longitudinal edges.

The stent can be formed into a particular pattern known in the art for stents formed from metal sheets. One such pattern is a rolled locking design and is illustrated in FIG. **9**. The sheet is etched into a stent configuration that has a head portion **72** that includes one or more slots **74** for receipt of a like number of tail portions **76**. The tail portions are received into the slots so as to form a cylindrical loop. The tail end includes a plurality of teeth **78** adapted to cooperatively engage the slot of the head portion. When the teeth engage the slot, the tail is retained in place in an expanded state. Additionally, holes **80** are formed throughout the stent to reduce the metal-to-air ratio of the stent. The less metal in contact with the wall **14** of the vessel **16**, the better the blood compatibility of the stent.

Prior to deployment, the tail end is coiled into a retracted position. The tail is threaded through the slot and wound. It is expanded by a balloon according to principles that are well known in the art for delivering and implanting a stent. As the stent is expanded by a balloon during deployment it unwinds and the teeth lock into the slots at a desired radial diameter to prevent the stent from returning to its original retracted state.

A benefit of the coiled stent shown in FIG. **9** is that the stent **70** can be etched to have a minimal surface area that comes in contact with the walls of the vessel. This may be an important feature when it is desired to cover an entire portion of the walls of a blood vessel with a therapeutic agent because the coiled sheet metal stent can be configured to maintain maximum surface area contact with the wall of the blood vessel in contrast to wire stents.

With reference to FIG. **10**, another embodiment of the present invention is a sheet formed of sintered particles that are sintered to both sides **84** and **86** of a metal sheet **82**. The stent of FIG. **10** is similar in structure to the stent wire of FIG. **7** that has a solid core and has porous particles sintered to the core forming a porous outer layer. The solid core reinforces the strength of the metal. The metal sheet also provides a barrier through which a therapeutic agent cannot pass. Thus, a therapeutic agent loaded into the pores **92** on the top side of **84** the sheet permeates in a first direction **88** outward from the solid core. A therapeutic agent loaded into the pores **94** on the bottom side **86** of the solid wire permeates only in a second direction **90** opposite to the direction of the therapeutic agent loaded into the pores on the top side.

When a stent as shown in FIG. **10** is looped into a cylindrical formation and placed into a vessel, only the top side **84**, which is directed radially outward, engages the walls of the vessel. The bottom side **94** faces radially inward and does not come in contact with the walls of the vessel. Thus, if it is desired, a first therapeutic agent can be loaded into the top side to treat the tissue in the wall of the vessel. A second therapeutic agent can be loaded into the bottom side to prevent coagulation of the blood flowing in the vessel. Additionally, the stent can be formed so that particles are sintered only to one side of the stent. A therapeutic agent is loaded into the sintered metal on the porous side of the stent. When a stent is formed from a one-sided porous stent, it can be oriented radially outward to deliver a therapeutic agent to the tissue in the wall of the stent.

FIG. **11** illustrates a cross-sectional view of a stent wire of strut according to one embodiment of the invention. The sheet has a plurality of porous cavities or pores **98**. A therapeutic agent is loaded into the pores of the sintered metal. Then, a coating **100** is applied to the sintered metal. The coating may be used for several purposes as illustrated hereinafter.

With reference to FIG. **12**, another embodiment of the invention is shown wherein the stent is formed of a sintered sheet **104** of metal having core **106** formed of large diameter particles **108** that form large pores. The core layer **106** is sandwiched between two layers **110** and **112** formed of smaller diameter particles **114** or particles that form smaller diameter pores. Such a sheet is formed by orienting a middle or core layer **106** of large diameter particles along a plane. A top layer of smaller diameter particles is arranged in a plane parallel to and above the middle layer. A bottom layer of particles are arranged in a plane parallel to and below the middle layer. The three layers are pressed together and sintered into a single sheet. The sheet can then be cut or etched into a stent configuration.

While one of the benefits of the present invention is to provide a stent that does not require a coating for the purpose

of delivering a therapeutic agent to the blood vessel, the application of a coating after a therapeutic agent is loaded into the pores of the sintered metal does not defeat the utility of the present invention. For example, when a therapeutic agent is loaded into the pores of the stent and into a polymeric coating, the profile of the polymeric coating can be reduced. Alternatively, a larger dosage of a therapeutic agent can be delivered to the site of stent implantation. Additional benefits are observed by loading a stent with a therapeutic agent in the pores of the metal and then further applying a coating to the stent. Furthermore, even if a coating is applied to the stent, the principles of reducing profile and reinforcing the stent are still apparent because a greater volume of therapeutic agent can be delivered by a coated sintered stent than a coated, solid stent have comparable dimensions.

The polymeric material that coats a sintered metal stent of the invention preferably comprises a biodegradable, bioabsorbable polymeric film that is capable of being loaded with and capable of releasing therapeutic drugs. The polymeric coatings preferably include, but are not limited to, polycaprolactone (PCL), poly-DL-lactic acid (DL-PLA) and poly-L-lactic acid (L-PLA) or lactide. Other biodegradable, bioabsorbable polymers such as polyorthoesters, polyiminocarbonates, aliphatic polycarbonates, and polyphosphazenes may also be suitable, and other non-degradable polymers capable of carrying and delivering therapeutic drugs may also be suitable. Examples of non-degradable synthetic polymers are Parylene®, Parylast® (from Advanced Surface Technology of Billerica, Mass.), polyurethane, polyethylene, polyethylene teraphthalate, ethylene vinyl acetate, silicone and polyethylene oxide (PEO). The polymeric layers, according to one embodiment is to be loaded with a pharmacologic agent for use in localized drug therapy. As used in this description, the terms biodegradable, bioabsorbable, reabsorbable, degradable, and absorbable are meant to encompass materials that are broken down and gradually absorbed or eliminated by the body, whether these processes are due to hydrolysis, metabolic processes, bulk or surface erosion. In each of the foregoing embodiments, one polymeric layer is preferably 0.002 inches thick.

The thin polymeric films used to coat the stent are preferably first intermixed with the drug or drugs to be delivered, and then are typically laminated or solvent cast to the surface of the metal structural member. Lamination processing methods and temperatures can vary widely depending on the polymers used and the temperature sensitivity of the loaded drugs. Alternatively, the metal structure of the stent can be encapsulated in the layers of polymeric material by solvent casting, melt processing, insert molding, and dip coating.

In one embodiment of the present invention, the membrane is bioabsorbable, but no therapeutic agent is loaded into the polymer. The coating **100** dissolves after implantation and this delays the time that a therapeutic agent is released into the vasculature of a patient. The thickness of the coating as well as the rate at which the coating is bioabsorbed determines the length of time that the stent is mounted into the vascular before a therapeutic agent is delivered from the pores of the stent. Additionally, a therapeutic agent can be loaded into the bioabsorbable coating. Thus a therapeutic agent will be delivered to the stent at a rate determined by the bioabsorbability of the coating. Once the bioabsorbable material has completely dissolved, the therapeutic agent in the pores can be delivered at a rate determined by the pore size and porosity.

In another embodiment, it is preferred that the coating **100** is permeable and non-absorbable. In such circumstances, the rate at which the drugs permeate into the tissue is controlled by the physical properties of the particular coating selected. Additionally, the coating may be selected to reduce restenosis, thrombosis or other tissue inflammation. For example, a heparin coating is known in the art to reduce blood clotting. Heparin, when coated on a stent reduces clotting of blood on the surface of the stent. The heparin coating is affixed to the surface of the stent through ionic bonding, end point attaching, or photo-linking the heparin.

In yet another embodiment, a first therapeutic agent is loaded into the coating and a second therapeutic agent is loaded into the pores of the stent. This may be the case when a series of drug dosages or concentrations are needed. When such a stent is placed into the vasculature, the first therapeutic agent is absorbed first by the stent and a second therapeutic agent is absorbed later by the vasculature. This variation adds a further dimension to drug treatment allowing for sequential drug therapy at the site of placement of a stent.

It will be apparent from the foregoing that while particular forms of the invention have been illustrated and described, various modifications can be made without departing from the spirit and scope of the invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

What is claimed is:

1. A medicated stent comprising:

a metallic stent configured to maintain patency of a human vessel, the metallic stent having a plurality of porous cavities;

a therapeutic medication loaded into the porous cavities of the metallic stent; and

a polymeric coating over the surface of the metallic stent wherein the medication in the pores of the stent is a first medication, wherein the coating contains a second medication.

2. The stent of claim **1**, wherein the coating is approximately in the range of 0.0001 inches to 0.002 inches thick.

3. The stent of claim **1**, wherein the coating is a bio-polymer.

4. The stent of claim **3**, wherein the bio-polymer is polylactic acid or fibrin.

5. The stent of claim **1**, wherein the coating is a synthetic polymer.

6. The stent of claim **5**, wherein the coating of the group comprising polyurethane, polyethylene teraphthalate, polyethylene, ethlene vinyl acetate, silicone or polyethylene oxide.

7. The stent of claim **1**, wherein the coating is a hydrogel.

8. The stent of claim **1**, wherein the coating is a heparin coating.

9. The stent of claim **1**, wherein the coating is an ionic heparin coating that is ionic bonded.

10. The stent of claim **1**, wherein the coating is an end point attached heparin coating.

11. The stent of claim **1**, wherein the coating is a photo-linked heparin coating.

12. The stent of claim **1**, wherein the coating is porous and the pores are sized to permit controlled release of the medication through the pores.

13. The stent of claim **1**, wherein the coating is capable of being dissolved by the body fluids.

14. The stent of claim **1**, wherein the coating is configured to reduce the porosity of the stent.

15. The stent of claim **1**, wherein the coating is configured to improve the blood compatibility of the stent.

16. The stent of claim 1, wherein the first medication is an antithrombogenic material.

17. The stent of claim 16, wherein the first medication is of the group comprising heparin, ticlopodine, coumadin, dipyridamole, aspirin, forskolin.

18. The stent of claim 16, wherein the first medication is an $GPII_bIII_a$ blocker.

19. The stent of claim 16, wherein the first medication is an anti-coagulant.

20. The stent of claim 16, wherein the first medication is an anti-fibrin agent.

21. The stent of claim 16, wherein the first medication is an anti-thrombin agent.

22. The stent of claim 16, wherein the first medication is an anti-platelet agent.

23. The stent of claim 16, wherein the first medication is an anti-proliferative agent.

24. The stent of claim 16, wherein the first medication is a radioactive material.

25. The stent of claim 16, wherein the first medication is a vaso-active drug.

26. The stent of claim 16, wherein the first medication promotes endothelialization.

27. The stent of claim 16, wherein the first medication is an anti-inflammatory agent.

* * * * *